5-SUBSTITUTED 7,9-DIFLUORO-5*H*-CHROMENO[3,4-*f*]QUINOLINE COMPOUNDS AS SELECTIVE PROGESTERONE RECEPTOR MODULATOR COMPOUNDS

Related Applications

This application claims the benefit of priority of U.S. Provisional Application Ser. No. 60/417,968 filed October 11, 2002, the entire disclosure of which is incorporated herein by reference.

Field of the Invention

This invention relates to 5-substituted 7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline compounds that may be highly potent receptor- and tissue-selective modulators (*i.e.* agonists, partial agonists and antagonists) of progesterone receptors and to methods for the making and use of such compounds.

Background of the Invention

Progesterone receptor (PR) modulators have been widely used in regulation of female reproduction systems and in treatment of female hormone dependent diseases. The effectiveness of known steroidal PR modulators is often tempered by their undesired side-effect profile, particularly during long-term administration. For example, the effectiveness of synthetic progestins as female birth control agents or hormone replacement therapies must be weighed against the increased risk of breast cancer due to progestins' proliferative activity in breast tissue. Similarly, the

progesterone antagonist, mifepristone (RU486), if administered for chronic indications, such as uterine fibroids, endometriosis and certain hormone-dependent cancers, could lead to homeostatic imbalances in a patient due to its inherent cross-reactivity as a glucocorticoid receptor (GR) antagonist. Accordingly, identification of compounds that have good receptor-selectivity for PR over other steroid hormone receptors as well as good tissue-selectivity (*e.g.* selectivity for uterine tissue over breast tissue) would be of significant value in the improvement of women's health.

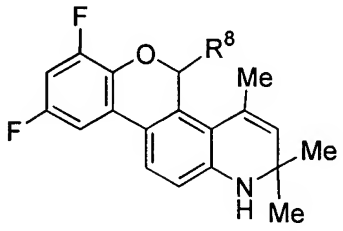
A group of nonsteroidal molecules which contain a di- or tetra-hydroquinoline ring as core pharmacophore (U.S. Patent Nos. 5,693,646; 5,693,647 and 5,696,127; PCT Int. Publication Nos. WO 99/41256 A1 and WO 99/41257 A1) have been described as steroid hormone receptor modulator compounds.

The entire disclosures of the patents, publications and references referred to herein are incorporated by reference herein and are not admitted to be prior art.

Summary of the Invention

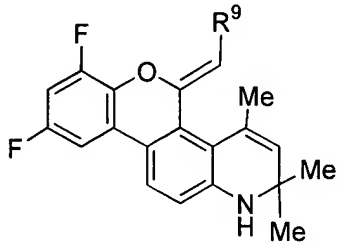
The present invention is directed to compounds, pharmaceutical compositions, and methods for modulating processes mediated by Progesterone Receptor. More particularly, the invention relates to 5-substituted 7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline compounds and compositions which may be high affinity, high specificity agonists, partial agonists (*i.e.*, partial activators and/or tissue-specific activators) and/or antagonists for progesterone receptors. Also provided

are methods of making such compounds and pharmaceutical compositions. Compounds of the present invention may be represented by the formulae:



(I)

or



(II)

wherein:

R^8 is selected from the group of C_1–C_{12} alkyl, C_1–C_{12} heteroalkyl, C_1–C_{12} haloalkyl, C_2–C_{12} alkenyl, C_2–C_{12} heteroalkenyl, C_2–C_{12} haloalkenyl, C_2–C_{12} alkynyl, C_2–C_{12} heteroalkynyl, C_2–C_{12} haloalkynyl, aryl and heteroaryl, wherein said alkyl, heteroalkyl, haloalkyl, alkenyl, heteroalkenyl, haloalkenyl, heteroalkynyl, haloalkynyl, alkynyl, aryl and heteroaryl radicals are optionally substituted;

R^9 is selected from the group of hydrogen, F, Cl, Br, I, CN, C_1–C_8 alkyl, C_1–C_8 heteroalkyl, C_1–C_8 haloalkyl, C_2–C_8 alkenyl, C_2–C_8 heteroalkenyl, C_2–C_8 haloalkenyl, C_2–C_8 alkynyl, C_2–C_8 heteroalkynyl, C_2–C_8 haloalkynyl, aryl and heteroaryl, wherein

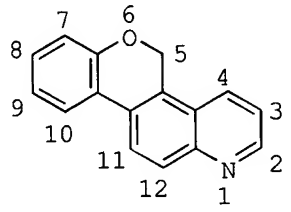
said alkyl, heteroalkyl, haloalkyl, alkenyl, heteroalkenyl, haloalkenyl, heteroalkynyl, haloalkynyl, alkynyl, aryl and heteroaryl radicals are optionally substituted;

and pharmaceutically acceptable salts and prodrugs thereof.

Definitions and Nomenclature

As used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise. Furthermore, in an effort to maintain consistency in the naming of compounds of similar structure but differing substituents, the compounds described herein are named according to the following general guidelines. The numbering system for the location of substituents on such compounds is also provided.

A 5*H*-chromeno[3,4-*f*]quinoline is defined by the following structure.



The term "alkyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain or cyclic alkyl radical typically having from 1 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having from 1 to about 6 carbon atoms as well as those having from 1 to about 4 carbon atoms. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-amyl, pentyl, hexyl, heptyl, octyl

and the like.

The term "alkenyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon double-bonds and having from 2 to about 18 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon double bonds and typically having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, 1,3-butadienyl and the like.

"Allyl" alone or in combination refers to $-CH_2-CH=CH_2$.

"Methylidene" alone or in combination refers to $=CH_2$.

The term "alkynyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon triple-bonds and typically having from 2 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon triple bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, butynyl and the like.

The term "heteroalkyl," "heteroalkenyl" and "heteroalkynyl" refer to alkyl, alkenyl and alkynyl radicals, as described above, in which one or more skeletal atoms

are heteroatoms such as, for example, oxygen, nitrogen, sulfur or combinations thereof. The terms heteroalkyl, heteroalkenyl and heteroalkynyl include radicals in which 1 to about 6 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof, as well as those in which 1 to 4 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof and those in which 1 to 2 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof.

The term "aryl," alone or in combination, refers to an optionally substituted aromatic ring system. The term aryl includes monocyclic aromatic rings, polyaromatic rings and polycyclic aromatic ring systems containing from to six about twenty carbon atoms. The term aryl also includes monocyclic aromatic rings, polyaromatic rings and polycyclic ring systems containing from six to about 12 carbon atoms, as well as those containing from 6 to about 10 carbon atoms. The polyaromatic and polycyclic aromatic rings systems may contain from two to four rings. Examples of aryl radicals include, without limitation, phenyl, biphenyl, naphthyl and anthryl ring systems.

The term "heteroaryl" refers to an optionally substituted aromatic ring system containing from about five to about 20 skeletal ring atoms and having one or more heteroatoms such as, for example, oxygen, nitrogen and sulfur. The term heteroaryl also includes optionally substituted aromatic ring systems having from 5 to about 12 skeletal ring atoms, as well as those having from 5 to about 10 skeletal ring atoms. The term heteroaryl may include five- or six-membered heterocyclic rings, polycyclic

heteroaromatic ring systems and polyheteroaromatic ring systems where the ring system has two, three or four rings. The terms heterocyclic, polycyclic heteroaromatic and polyheteroaromatic include ring systems containing optionally substituted heteroaromatic rings having more than one heteroatom as described above (*e.g.*, a six membered ring with two nitrogens), including polyheterocyclic ring systems of from two to four rings. The term heteroaryl includes ring systems such as, for example, furanyl, benzofuranyl, chromenyl, pyridyl, pyrrolyl, indolyl, quinolinyl, N-alkyl pyrrolyl, pyridyl-N-oxide, pyrimidyl, pyrazinyl, imidazolyl, pyrazolyl, oxazolyl, benzothiophenyl, purinyl, indolizinyl, thienyl and the like.

The terms haloalkyl, haloalkenyl, haloalkynyl and haloalkoxy include alkyl, alkenyl, and alkynyl structures, as described above, that are substituted with one or more fluorines, chlorines, bromines or iodines, or with combinations thereof.

The terms cycloalkyl, aryl, arylalkyl, heteroaryl, alkyl, alkynyl, alkenyl, haloalkyl and heteroalkyl include optionally substituted cycloalkyl, aryl, arylalkyl, heteroaryl, alkyl, alkynyl, alkenyl, haloalkyl and heteroalkyl radicals.

The term "carbocycle" includes optionally substituted, saturated or unsaturated, three- to eight-membered cyclic structures in which all of the skeletal atoms are carbon.

The term "heterocycle" includes optionally substituted, saturated or unsaturated, three- to eight-membered cyclic structures in which one or more skeletal atoms is

oxygen, nitrogen, sulfur, or combinations thereof.

The term "acyl" includes alkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl substituents attached to a compound via a carbonyl functionality (*e.g.*, -CO-alkyl, -CO-aryl, -CO-arylalkyl or -CO-heteroarylalkyl, etc.).

The term "halogen" includes F, Cl, Br and I.

The term "mediate" means affect or influence, frequently indirectly or via some intervening action. Thus, for example, conditions mediated by a progesterone receptor are those in which a progesterone receptor plays a role. Progesterone receptors are known to play a role in conditions including, for example, infertility, contraception, pregnancy maintenance and termination, female hormone deficiency, female sexual dysfunction, dysfunctional uterine bleeding, endometriosis, mood disorder, osteoporosis, and hormone-dependent cancers.

The term "receptor-selectivity" refers to the conditions where a compound displays modulating activity towards one or more particular receptors (*e.g.*, a progesterone receptors) while displaying substantially less or no cross-reactivity towards one or more different receptors (*e.g.*, glucocorticoid receptors). Thus, for example, selective compounds of the present invention may display modulating activity towards progesterone receptors without displaying substantial cross-reactivity towards

another steroid hormone receptors. Compounds may be selective for a single receptor, group of similar receptors or multiple receptors.

The term "tissue-selectivity" refers to compounds that display substantial modulating activity in one tissue (*e.g.*, uterine tissue) while displaying lesser modulating activity in at least one other tissue (*e.g.*, breast tissue). Thus, for example, tissue-selective compounds of the present invention may display substantial modulating activity in uterine and vaginal tissues with lesser modulating activity (partial agonistic or partial antagonistic) in breast tissues relative to the activities of the marketed steroidal progestins in all of the target tissues.

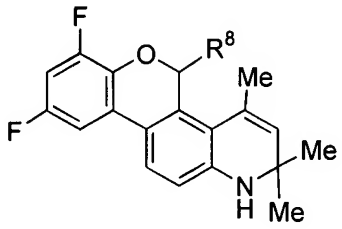
The term "modulate" means affect or influence, for example, the amount, degree or proportion. Thus, compounds that "modulate" a receptor affect the activity, either positively or negatively, of that receptor. The term may be used to refer to the activity of compounds of a receptor as, for example, an agonist, partial agonist or antagonist. The term also may be used to refer to the effect that a compound has on a physical and/or physiological condition of an individual. For example, certain compounds of the present invention may be used to modulate fertility in an individual. That is, certain compounds of this invention may be used to increase the fertility of an individual, while other compounds of this invention may be used to decrease the fertility of an individual.

A compound that binds to a receptor and mimics the effect of the native or endogenous ligand is referred to as an "agonist," while a compound that binds to a

receptor and inhibits or has an effect that is opposite that of the native or endogenous ligand is called an "antagonist." "Partial agonists" give an effect of the same type as the native or endogenous ligand, but of a lower magnitude, while "partial antagonists" are incompletely inhibitory or opposite that of the native or endogenous ligand.

Detailed Description of the Invention

Compounds of the present invention may be represented by the formulae:



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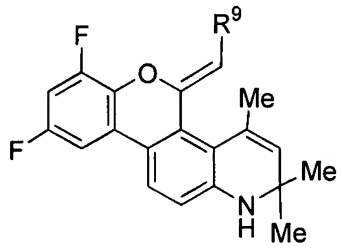
or



(II)

wherein:

R^8 is selected from the group of C_1–C_{12} alkyl, C_1–C_{12} heteroalkyl, C_1–C_{12} haloalkyl, C_2–C_{12} alkenyl, C_2–C_{12} heteroalkenyl, C_2–C_{12} haloalkenyl, C_2–C_{12} alkynyl, C_2–C_{12} heteroalkynyl, C_2–C_{12} haloalkynyl, aryl and heteroaryl, optionally substituted with one or more substituents independently selected from the group of hydrogen, C_1–

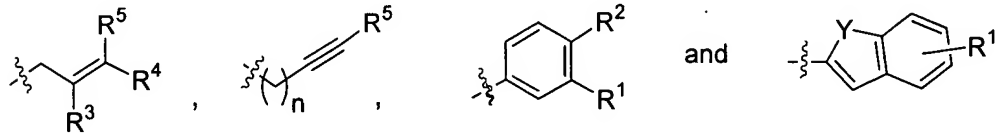
C_4 alkyl, F, Cl, Br, I, CN, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CF_3, $C(O)CH_3$, CO_2CH_3, $C(O)NH_2$, OR^{10}, SR^{10}, and $NR^{10}R^{11}$;

R^9 is selected from the group of hydrogen, F, Cl, Br, I, CN, C_1–C_8 alkyl, C_1–C_8 heteroalkyl, C_1–C_8 haloalkyl, C_2–C_8 alkenyl or cycloalkenyl, C_2–C_8 heteroalkenyl, C_2–C_8 haloalkenyl, C_2–C_8 alkynyl, C_2–C_8 heteroalkynyl, C_2–C_8 haloalkynyl, aryl and heteroaryl optionally substituted with one or more substituents independently selected from the group of hydrogen, C_1–C_4 alkyl, F, Cl, Br, I, CN, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CF_3, $C(O)CH_3$, CO_2CH_3, $C(O)NH_2$, OR^{10}, SR^{10}, and $NR^{10}R^{11}$; and

R^{10} and R^{11} each independently is hydrogen or C_1-C_4 alkyl; and

pharmaceutically acceptable salts and prodrugs thereof.

In one embodiment, R^8 is selected from the group of:



R^1 and R^2 each independently is selected from the group of hydrogen, F, Cl, Br and C_1–C_4 alkyl;

R^3 through R^5 each independently is selected from the group of hydrogen, F, Cl and C_1–C_4 alkyl;

R^6 is selected from the group of hydrogen, F, Cl, Br, C_1–C_4 alkyl, OR^{10}, SR^{10}, and $NR^{10}R^{11}$;

R^7 is hydrogen, F, or Cl;

R^{10} and R^{11} each independently is hydrogen or C_1–C_4 alkyl;

n is 0 or 1;

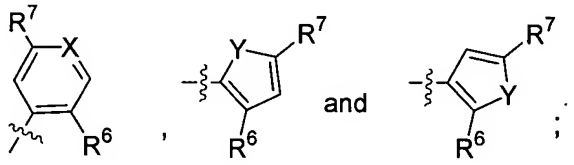
X is CH or N; and

Y is selected from the group of O, S, and NR^{10};

and pharmaceutically acceptable salts and prodrugs thereof.

In another embodiment, R^6 is selected from the group of F, Me, Et, OMe, OEt, SMe, and NMe_2.

In another embodiment, R^9 is selected from the group of:



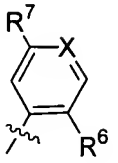
R^6 is selected from the group of hydrogen, F, Cl, Br, C_1–C_4 alkyl, OR^{10}, SR^{10}, and $NR^{10}R^{11}$;

X is CH or N; and

R^7 is hydrogen, F, or Cl; and

Y is selected from the group of O, S, and NR^{10}.

In another embodiment, R^9 is



;

R^6 is selected from the group of hydrogen, F, Cl, Br, C_1–C_4 alkyl, OR^{10}, SR^{10}, and $NR^{10}R^{11}$;

R^7 is hydrogen, F, or Cl; and

X is CH or N.

In the following table, the inventors contemplate any combination of the following Markush groups and those described above for the various variables.

Table A. Table of Markush Groups by Variable

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R_1	H, F, Cl, Br and C_1–C_4 alkyl	F, Cl, Br and C_1–C_2 alkyl	F, Cl, Br and methyl	F and Cl
R_2	H, F, Cl, Br and C_1–C_4 alkyl	F, Cl, Br and C_1–C_2 alkyl	F, Cl, Br and methyl	F and Cl
R_3	H, F, Cl, and C_1–C_4 alkyl	F, Cl and C_1–C_2 alkyl	F, Cl and methyl	F and Cl
R_4	H, F, Cl, and C_1–C_4 alkyl	F, Cl and C_1–C_2 alkyl	F, Cl and methyl	F and Cl
R_5	H, F, Cl, and C_1–C_4 alkyl	F, Cl and C_1–C_2 alkyl	F, Cl and methyl	F and Cl
R_6	H, F, Cl, Br, C_1–C_4 alkyl, OR^{10}, SR^{10}, and $NR^{10}R^{11}$	H, F, Cl, C_1–C_4 alkyl, OMe, OEt, NHMe, and NMe_2	F, Me, Et, OMe, OEt, SMe, and NMe_2	F and methyl
R_7	H, F, and Cl	F and Cl		F

	Markush Group A	**Markush Group B**	**Markush Group C**	**Markush Group D**
R_8	C_1–C_{12} alkyl, C_1–C_{12} heteroalkyl, C_1–C_{12} haloalkyl, C_2–C_{12} alkenyl, C_2–C_{12} heteroalkenyl, C_2–C_{12} haloalkenyl, C_2–C_{12} alkynyl, C_2–C_{12} heteroalkynyl, C_2–C_{12} haloalkynyl, aryl and heteroaryl, optionally substituted with one or more substituents independently selected from the group of H, C_1–C_4 alkyl, F, Cl, Br, I, CN, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CF_3, $C(O)CH_3$, CO_2CH_3, $C(O)NH_2$, OR^{10}, SR^{10} and $NR^{10}R^{11}$	C_1–C_8 alkyl, C_1–C_8 heteroalkyl, C_1–C_8 haloalkyl, C_2–C_8 alkenyl, C_2–C_8 heteroalkenyl, C_2–C_8 haloalkenyl, C_2–C_8 alkynyl, C_2–C_8 heteroalkynyl, C_2–C_8 haloalkynyl, aryl and heteroaryl, optionally substituted with one or more substituents independently selected from the group of H, C_1–C_4 alkyl, F, Cl, Br, I, CN, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CF_3, $C(O)CH_3$, CO_2CH_3, $C(O)NH_2$, OR^{10}, SR^{10} and $NR^{10}R^{11}$	aryl and heteroaryl, optionally substituted with one or more of H, C_1–C_4 alkyl, F, Cl, Br, CN, NH_2, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CF_3, $C(O)CH_3$, OR^{10}, SR^{10} and $NR^{10}R^{11}$	C_1–C_4 alkyl, C_1–C_4 heteroalkyl, C_1–C_4 haloalkyl, C_2–C_4 alkenyl, C_2–C_4 heteroalkenyl, C_2–C_4 haloalkenyl, C_2–C_4 alkynyl, C_2–C_4 heteroalkynyl, and C_2–C_4 haloalkynyl

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R_9	H, F, Cl, Br, I, CN, C_1–C_8 alkyl, C_1–C_8 heteroalkyl, C_1–C_8 haloalkyl, C_2–C_8 alkenyl or cycloalkenyl, C_2–C_8 heteroalkenyl, C_2–C_8 haloalkenyl, C_2–C_8 alkynyl, C_2–C_8 heteroalkynyl, C_2–C_8 haloalkynyl, aryl and heteroaryl, optionally substituted with one or more substituents independently selected from H, C_1–C_4 alkyl, F, Cl, Br, I, CN, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CF_3, $C(O)CH_3$, CO_2CH_3, $C(O)NH_2$, OR^{10}, SR^{10}, and $NR^{10}R^{11}$	aryl and heteroaryl, optionally substituted with one or more substituents independently selected from H, C_1–C_4 alkyl, F, Cl, Br, CN, NH_2, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, OR^{10}, SR^{10}, and $NR^{10}R^{11}$	H, Br, Cl, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, C_1–C_4 haloalkyl, C_2–C_4 alkenyl, C_2–C_4 heteroalkenyl, C_2–C_4 haloalkenyl, C_2–C_4 alkynyl and C_2–C_4 heteroalkynyl, C_2–C_4 haloalkynyl	
R_{10}	H and C_1–C_4 alkyl		H and methyl	H
R_{11}	H and C_1–C_4 alkyl		H and methyl	H
n	0 or 1			
X	CH or N			N
Y	O, S, and NR^{10}	O and S		S

In one aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a progesterone receptor modulator compound of formulae I or II shown above wherein R^1 through R^{11}, n, X, Y, have the same definitions as given above.

In a further aspect, the present invention comprises a method of modulating a process mediated by progesterone receptors comprising administering to a patient having a condition mediated by progesterone receptors an effective amount of a compound of the formulae I or II shown above, wherein R^1 through R^{11}, n, X, Y, have the same definitions as those given above.

Any of the compounds of the present invention can be synthesized as pharmaceutically acceptable salts for incorporation into various pharmaceutical compositions. As used herein, pharmaceutically acceptable salts include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, hydrofluoric, sulfuric, citric, maleic, acetic, lactic, nicotinic, succinic, oxalic, phosphoric, malonic, salicylic, phenylacetic, stearic, pyridine, ammonium, piperazine, diethylamine, nicotinamide, formic, urea, sodium, potassium, calcium, magnesium, zinc, lithium, cinnamic, methylamino, methanesulfonic, picric, tartaric, triethylamino, dimethylamino, and tris(hydroxymethyl)aminomethane. Additional pharmaceutically acceptable salts are known to those skilled in the art.

PR agonist, partial agonist and antagonist compounds of the present invention may be particularly useful for female hormone replacement therapy and as modulators of fertility (*e.g.*, as contraceptives, contragestational agents or abortifacients, *in vitro* fertilization, pregnancy maintenance), either alone or in conjunction with one or more estrogen receptor modulators. PR modulator compounds of this invention also may be used in the treatment of dysfunctional uterine bleeding, dysmenorrhea, endometriosis, leiomyomas (uterine fibroids), hot flushes, mood disorders, and meningiomas. The PR modulator compounds of this invention also may be used in the treatment of various hormone-dependent cancers, including, without limitation, cancers of ovaries, breast, endometrium and prostate. PR modulator compounds of this invention can also be used in treatment of female osteoporosis, either alone or in combination with one or more estrogen receptor modulators.

It will be understood by those skilled in the art that while the compounds of the present invention will typically be employed as selective agonists, partial agonists or antagonists, that there may be instances where a compound with a mixed steroid receptor profile is preferred. For example, use of a PR agonist (*i.e.*, progestin) in female contraception often leads to the undesired effects of increased water retention and acne flare ups. In this instance, a compound that is primarily a PR agonist, but also displays some AR and MR modulating activities, may prove useful. Specifically, the mixed MR effects would be useful to control water balance in the body, while the AR effects would help to control any acne flare ups that occur.

Furthermore, it will be understood by those skilled in the art that compounds of the present invention, including pharmaceutical compositions and formulations containing these compounds, can be used in a wide variety of combination therapies to treat the conditions and diseases described above. Thus, compounds of the present invention can be used in combination with other hormones and other therapies, including, without limitation, chemotherapeutic agents such as cytostatic and cytotoxic agents, immunological modifiers such as interferons, interleukins, growth hormones and other cytokines, hormone therapies, surgery and radiation therapy.

Representative PR modulator compounds (*i.e.*, agonists, partial agonists and antagonists) according to the present invention include:

7,9-difluoro-5(*Z*)-benzylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **10**);

7,9-difluoro-5(*Z*)-(2-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **12**);

7,9-difluoro-5(*Z*)-(2-chlorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **13**);

7,9-difluoro-5(*Z*)-(4-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **14**);

7,9-difluoro-5(*Z*)-(3-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **15**);

7,9-difluoro-5(*Z*)-(4-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **16**);

7,9-difluoro-5(*Z*)-(2,5-difluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **17**);

7,9-difluoro-5(*Z*)-(2-methoxybenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **18**);

7,9-difluoro-5(*Z*)-(2-methyl-5-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **19**);

7,9-difluoro-5(*Z*)-(3-methyl-4-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **20**);

7,9-difluoro-5(*Z*)-(2-methyl-3-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **21**);

7,9-difluoro-5(*Z*)-(3-methyl-2-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **22**);

7,9-difluoro-5(*Z*)-(2,3-dimethylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **23**);

7,9-difluoro-5(*Z*)-cyanomethylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **24**);

7,9-difluoro-5(*Z*)-hexylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **25**);

7,9-difluoro-5(*Z*)-(2-methoxy-5-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **26**);

7,9-difluoro-5(*Z*)-(2,4,5-trifluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **27**);

7,9-difluoro-5-methylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **28**);

7,9-difluoro-5(*Z*)-bromomethylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **29**);

7,9-difluoro-5(*Z*)-(3-thienylmethylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **30**);

7,9-difluoro-5(*Z*)-(2-thienylmethylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **31**);

(±)-7,9-difluoro-5-methoxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **32**);

(±)-7,9-difluoro-5-phenyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **33**);

(±)-7,9-difluoro-5-(3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **34**);

(±)-7,9-difluoro-5-(1,3-benzodioxol-5-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **35**);

(±)-7,9-difluoro-5-(4-bromophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **36**);

(±)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **37**);

(-)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **38**);

(+)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **39**);

(±)-7,9-difluoro-5-(3-fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **40**);

(±)-7,9-difluoro-5-(3-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **41**);

(±)-7,9-difluoro-5-(3-bromophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **42**);

(±)-7,9-difluoro-5-(4-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **43**);

(±)-7,9-difluoro-1,2-dihydro-2,2,4,5-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **44**);

(±)-7,9-difluoro-5-(2-oxo-2-phenylethyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **45**);

(±)-7,9-difluoro-5-ethyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **46**);

(±)-7,9-difluoro-5-ethenyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **47**);

(±)-7,9-difluoro-5-(2-oxo-3-butenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **48**);

Methyl (±)-7,9-difluoro-1,2-dihydro-α,α,2,2,4-pentamethyl-5*H*-chromeno[3,4-*f*]quinoline-5-ethanoate (Compound **49**);

(±)-7,9-difluoro-5-ethynyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **50**);

(±)-7,9-difluoro-5-cyano-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **51**);

(±)-7,9-difluoro-5-butyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **52**);

(±)-7,9-difluoro-5-(2-thienyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **53**);

(±)-7,9-difluoro-5-(2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **54**);

(±)-7,9-difluoro-5-allyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **55**);

(±)-7,9-difluoro-5-[3-(trifluoromethyl)phenyl]-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **56**);

Ethyl (±)-7,9-difluoro-1,2-dihydro-α-methylene-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline-5-propanoate (Compound **57**);

(±)-7,9-difluoro-1,2-dihydro-β-methylene-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline-5-propanol (Compound **58**);

(±)-7,9-difluoro-1,2-dihydro-β-methylene-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline-5-propanol acetate(Compound **59**);

(±)-7,9-difluoro-5-(1-methylethenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **60**);

(±)-7,9-difluoro-5-(N-methyl-2-pyrrolyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **61**);

(±)-7,9-difluoro-5-phenylethynyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **62**);

(±)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **63**);

(-)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **64**);

(+)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **65**);

(±)-7,9-difluoro-5-(5-methyl-2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **66**);

(±)-7,9-difluoro-5-(2-benzo[b]furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **67**);

(±)-7,9-difluoro-5-[4-(dimethylamino)phenyl]-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **68**);

(±)-7,9-difluoro-5-(5-methyl-2-thienyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **69**);

(±)-7,9-difluoro-5-(5-methoxy-2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **70**);

(±)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **71**);

(-)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **72**);

(+)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **73**);

(±)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **74**);

(-)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **75**);

(+)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **76**);

(±)-7,9-difluoro-5-(4,5-dimethyl-2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **77**);

(±)-7,9-difluoro-5-(2-methyl-1-propenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **78**);

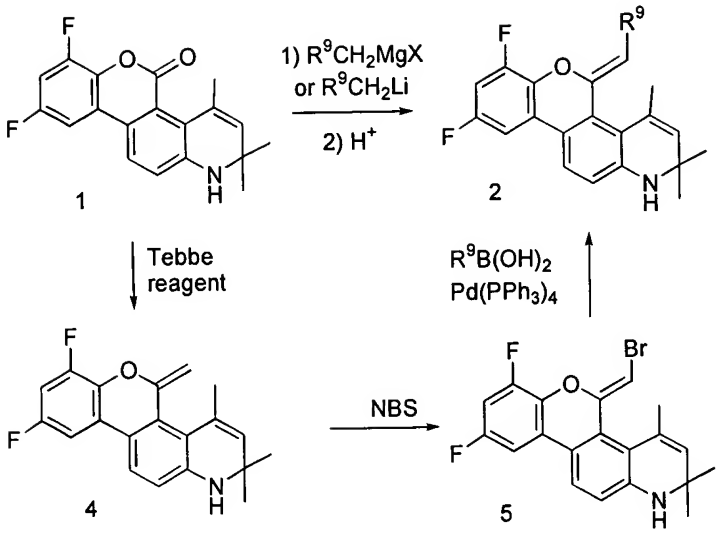
(±)-7,9-difluoro-5-(3,4-dimethyl-2-thienyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **79**);

(±)-7,9-difluoro-5-(3-(3-bromophenyl)phenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **80**); and

7,9-difluoro-5(*Z*)-(2-methylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **81**).

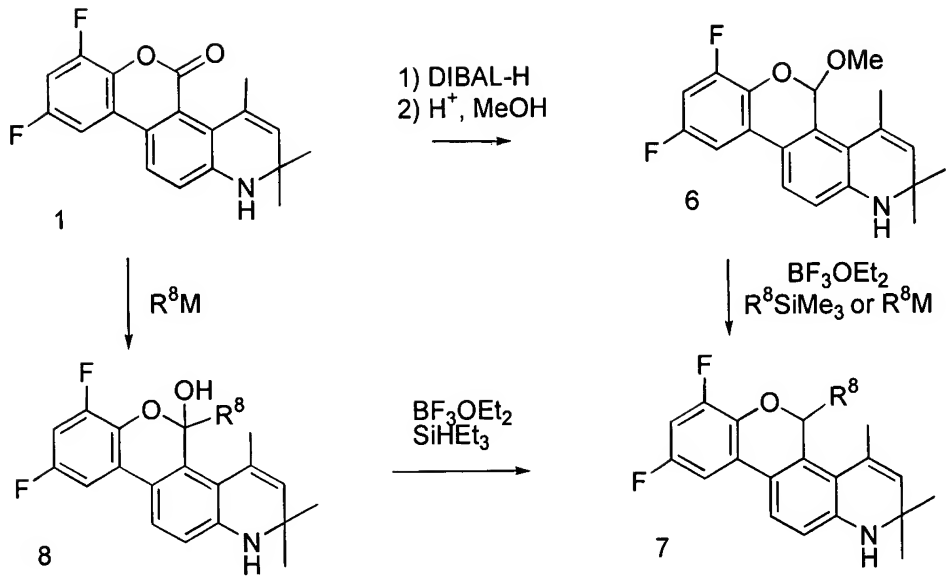
The sequence of steps for the general schemes to synthesize the compounds of the present invention is shown below. In each of the Schemes the R groups (*e.g.*, R^8, R^9, *etc.*) correspond to the specific substitution patterns noted in the Examples. However, it will be understood by those skilled in the art that other functionalities disclosed herein at the indicated positions of compounds of formulae I and II also comprise potential substituents for the analogous positions on the structures within the Schemes. In a further aspect, the present invention contains a novel process for the preparation of the compounds of the present invention.

Scheme I



The process of Scheme I begins with addition of organolithium or Grignard reagents to lactones **1** followed by the treatment with a Lewis acid, such as p-toluenesulfonic acid, to produce compounds of structure **2**. An alternative route starts with the treatment of lactone **1** with Tebbe reagent to provide compound **4**. Bromination with NBS affords the bromomethylidene **5**. Palladium catalyzed Suzuki reaction of compound **5** with a boronic acid gives the methylidene derivatives of structure **2**.

Scheme II



Scheme II describes the synthesis of the 5-alkyl/aryl analogues **7**. Reduction of lactone **1** with DIBAL-H followed by acid catalyzed methylation provides lactal intermediates **6**. Treatment of the lactal **6** with a nucleophile in the presence of a Lewis acid, such as BF_3-OEt_2, affords the final products of structure **7**. Alternatively, addition of a nucleophile directly to lactone 1 affords hemiacetals 8, which are treated with silane in the presence of a Lewis acid leading to the same products 7.

The compounds of the present invention also include racemates, stereoisomers and mixtures of said compounds, including isotopically-labeled and radio-labeled compounds. Such isomers can be isolated by standard resolution techniques, including fractional crystallization and chiral column chromatography.

As noted above, PR modulator compounds of the present invention can be combined in a mixture with a pharmaceutically acceptable carrier to provide pharmaceutical compositions useful for treating the biological conditions or disorders noted herein in mammalian, and particularly in human patients. The particular carrier employed in these pharmaceutical compositions may take a wide variety of forms depending upon the type of administration desired. Suitable administration routes include enteral (*e.g.,* oral), topical, suppository, inhalable and parenteral (*e.g.,* intravenous, intramuscular and subcutaneous).

In preparing the compositions in oral liquid dosage forms (*e.g.*, suspensions, elixirs and solutions), typical pharmaceutical media, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be employed. Similarly, when preparing oral solid dosage forms (*e.g.*, powders, tablets and capsules), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like will be employed. Due to their ease of administration, tablets and capsules represent a desirable oral dosage form for the pharmaceutical compositions of the present invention.

For parenteral administration, the carrier will typically comprise sterile water, although other ingredients that aid in solubility or serve as preservatives, may also be included. Furthermore, injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like will be employed.

For topical administration, the compounds of the present invention may be formulated using bland, moisturizing bases, such as ointments or creams. Examples of suitable ointment bases are petrolatum, petrolatum plus volatile silicones, lanolin and water in oil emulsions such as Eucerin™, available from Beiersdorf (Cincinnati, Ohio). Examples of suitable cream bases are Nivea™ Cream, available from Beiersdorf (Cincinnati, Ohio), cold cream (USP), Purpose Cream™, available from Johnson & Johnson (New Brunswick, New Jersey), hydrophilic ointment (USP) and Lubriderm™, available from Warner-Lambert (Morris Plains, New Jersey).

The pharmaceutical compositions and compounds of the present invention will generally be administered in the form of a dosage unit (*e.g.*, tablet, capsule, etc.). The compounds of the present invention generally are administered in a daily dosage of from about 1 μg/kg of body weight to about 50 mg/kg of body weight. Typically, the compounds of the present invention are administered in a daily dosage of from about 2 μg/kg to about 25 mg/kg of body weight. Preferably, the compounds of the present invention are administered in a daily dosage of from about 10 μg/kg to about 5 mg/kg body weight. As recognized by those skilled in the art, the particular quantity of pharmaceutical composition according to the present invention administered to a patient will depend upon a number of factors, including, without limitation, the biological activity desired, the condition of the patient, and tolerance for the drug.

Compounds of this invention also have utility when radio- or isotopically-labeled as ligands for use in assays to determine the presence of PR in a cell background or extract. Such compounds are particularly useful due to their ability to selectively activate progesterone receptors, and can therefore be used to determine the presence of such receptors in the presence of other steroid receptors or related intracellular receptors.

Compounds and pharmaceutical compositions of the present invention may be extremely potent activators of PR. For example, compounds and compositions of the present invention may display 50% maximal activation of PR at a concentration of less than 50 nM. Some compounds and compositions of the present invention may display 50% maximal activation of PR at a concentration of less than 20 nM, and some may display such activity at a concentration of 10 nM or less. In addition, the compounds of the present invention may be tissue-selective modulators. For example, the compounds of this invention may suppress estrogen-induced endometrial stimulation in uterus equally efficacious as marketed steroidal modulator compounds but display reduced proliferative activity or antagonized endogenous hormone induced proliferative activity in breasts.

The invention will be further illustrated by reference to the following non-limiting Examples.

EXAMPLE 1

Preparation of 7,9-difluoro-5(*Z*)-benzylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **10**, Structure **2** of Scheme I, where R^9 = phenyl).

General procedure I for preparing 5(*Z*)-substituted methylidene compounds (Structure **2** of Scheme I) from lactones (Structure **1** of Scheme I) and a Grignard or organolithium reagent. To a solution (0.2 – 1.0 M) of lactone **1** in THF was added a freshly prepared Grignard or organolithium solution (3 - 5 equiv.). The reaction mixture was stirred for 1-12 h until the starting material was consumed and then was poured into ice-cold 50% NH_4Cl and extracted with EtOAc (2×). The extracts were washed with brine (3×), dried (Na_2SO_4) and concentrated. A solution (0.2 – 0.5 M) of the crude lactol intermediate in CH_2Cl_2 was treated with a catalytic amount of p-toluenesulfonic acid at room temperature for 3 h, quenched with saturated $NaHCO_3$ and extracted with EtOAc (2×). The extracts were washed with brine (3×), dried (Na_2SO_4), and concentrated. Flash chromatography (silica gel, EtOAc–hexane 2% to 10% gradient) of the crude mixture afforded the final product in good yield. To prevent photoisomerization of the benzylidene analogues, the dehydration step and the work-up should be carried out in a light-controlled environment.

Compound **10** was prepared from benzyl Grignard and 7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound **11**, structure **1** of Scheme I)

according to the general procedure as a yellow solid: ^{1}H-NMR (400 MHz, $CDCl_3$) 7.84 (d, J = 7.9, 2H), 7.40-7.36 (m, 4H), 7.20-7.14 (m, 1H), 6.76-6.71 (m, 1H), 6.66 (d, J = 8.4, 1H), 5.67 (s, 1H), 5.54 (s, 1H), 4.24 (bs, 1H), 2.18 (s, 3H), 1.35 (bs, 6H).

EXAMPLE 2

Preparation of 7,9-difluoro-5(*Z*)-(2-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **12**, Structure **2** of Scheme I, where R^9 = 2-fluorophenyl).

This compound was prepared in a similar fashion as that described in Example 1 from 2-fluorobenzyl Grignard reagent and Compound **11** (Structure **1** of Scheme I,) as a yellow solid: ^{1}H-NMR (400 MHz, $CDCl_3$) 8.44-8.38 (m, 1H), 7.39 (d, J = 8.4, 1H), 7.23-7.14 (m, 3H), 7.06-7.00 (m, 1H), 6.76-6.70 (m, 1H), 6.67 (d, J = 8.4, 1H), 6.00 (s, 1H), 5.56 (s, 1H), 4.25 (bs, 1H), 2.12 (s, 3H), 1.35 (bs, 6H).

EXAMPLE 3

Preparation of 7,9-difluoro-5(*Z*)-(2-chlorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **13**, Structure **2** of Scheme I, where R^9 = 2-chlorophenyl).

This compound was prepared in a similar fashion as that described in Example 1 from 2-chlorobenzyl Grignard reagent and Compound **11** (Structure **1** of Scheme I) as a yellow solid: ^{1}H-NMR (400 MHz, $CDCl_3$) 8.45 (d, J = 8.0, 1H), 7.39 (d, J = 8.5, 1H),

7.36-7.30 (m, 2H), 7.18-7.13 (m, 2H), 6.73-6.70 (m, 1H), 6.69 (d, J = 8.5, 1H), 6.25 (s, 1H), 5.56 (s, 1H), 4.27 (bs, 1H), 2.13 (s, 3H), 1.35 (bs, 6H).

EXAMPLE 4

Preparation of 7,9-difluoro-5(*Z*)-(4-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **14**, Structure **2** of Scheme I, where R^9 = 4-pyridyl).

This compound was prepared in a similar fashion as that described in Example 1 from 4-picolyl lithium and Compound **11** (Structure **1** of Scheme I) as a yellow solid: ^{1}H-NMR (400 MHz, $CDCl_3$) 8.59 (d, J = 5.8, 2H), 7.69 (d, J = 5.1, 2H), 7.44 (d, J = 8.5, 1H), 7.20-7.18 (m, 1H), 6.81-6.79 (m, 1H), 6.73 (d, J = 8.5, 1H), 5.63 (s, 1H), 5.58 (s, 1H), 4.31 (bs, 1H), 2.09 (d, J = 1.2, 3H), 1.37 (bs, 6H).

EXAMPLE 5

Preparation of 7,9-difluoro-5(*Z*)-(3-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **15**, Structure **2** of Scheme I, where R^9 = 3-fluorophenyl).

This compound was prepared in a similar fashion as that described in Example 1 from 3-fluorobenzyl Grignard reagent and Compound **11** (Structure **1** of Scheme I) as a yellow solid: ^{1}H-NMR (400 MHz, Acetone-d_6) 7.82–7.79 (ddd, J = 2.0, 2.0, 9.5, 1H),

7.66 (d, J = 8.5, 1H), 7.52-7.38 (m, 3H), 7.05-6.97 (m, 2H), 6.87 (d, J = 8.5, 1H), 6.10 (bs, 1H), 5.79 (s, 1H), 5.58 (s, 1H), 2.08 (s, 3H), 1.40 (bs, 6H).

EXAMPLE 6

Preparation of 7,9-difluoro-5(*Z*)-(4-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **16**, Structure **2** of Scheme I, where R^9 = 4-fluorophenyl).

This compound was prepared in a similar fashion as that described in Example 1 from 4-fluorobenzyl Grignard reagent and Compound **11** (Structure **1** of Scheme I) as a yellow solid: ^{1}H-NMR (400 MHz, Acetone-d_6) 7.92-7.88 (dd, J = 5.6, 8.9, 2H), 7.64 (d, J = 8.5, 1H), 7.46-7.42 (ddd, J = 2.1, 2.1, 9.5, 1H), 7.19-7.14 (dd, J = 8.7, 8.7, 2H), 6.98-6.96 (m, 1H), 6.84 (d, J = 8.5, 1H), 6.07 (bs, 1H), 5.76 (s, 1H), 5.57 (s, 1H), 2.08 (s, 3H), 1.31 (bs, 6H).

EXAMPLE 7

Preparation of 7,9-difluoro-5(*Z*)-(2,5-difluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **17**, Structure **2** of Scheme I, where R^9 = 2,5-difluorophenyl).

This compound was prepared in a similar fashion as that described in Example 1 from 2,5-difluorobenzyl Grignard reagent and Compound **11** (Structure **1** of Scheme I) as a yellow solid: ^{1}H-NMR (400 MHz, Acetone-d_6) 8.26-8.21 (m, 1H), 7.69 (d, J = 8.5,

1H), 7.51-7.47 (ddd, J = 2.4, 2.4, 9.9, 1H), 7.22-7.16 (ddd, J = 4.7, 9.3, 9.3, 1H), 7.09-7.00 (m, 2H), 6.90 (d, J = 8.4, 1H), 6.16 (bs, 1H), 6.03 (s, 1H), 5.59 (s, 1H), 2.10 (s, 3H), 1.30 (bs, 6H).

EXAMPLE 8

Preparation of 7,9-difluoro-5(*Z*)-(2-methoxybenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **18**, Structure **2** of Scheme I, where R^9 = 2-methoxyphenyl).

This compound was prepared in a similar fashion as that described in Example 1 from 2-methoxybenzyl Grignard reagent and Compound **11** (Structure **1** of Scheme I) as a yellow solid: ^{1}H-NMR (400 MHz, Acetone-d_6) 8.31-8.28 (dd, J = 1.6, 7.8, 1H), 7.61 (d, J = 8.5, 1H), 7.44-7.41 (ddd, J = 2.0, 2.0, 9.9, 1H), 7.26-7.22 (ddd, J = 1.7, 7.5, 7.5, 1H), 7.04-6.90 (m, 3H), 6.82 (d, J = 8.5, 1H), 6.26 (s, 1H), 6.12 (bs, 1H), 5.55 (s, 1H), 3.80 (s, 3H), 2.11 (s, 3H), 1.33 (bs, 6H).

EXAMPLE 9

Preparation of 7,9-difluoro-5(*Z*)-(2-methyl-5-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **19**, Structure **2** of Scheme I, where R^9 = 2-methyl-5-fluorophenyl).

This compound was prepared in a similar fashion as that described in Example 1 from 2-methyl-5-fluorobenzyl Grignard reagent and Compound **11** (Structure **1** of

Scheme I) as a yellow solid: ^{1}H-NMR (400 MHz, Acetone-d_6) 8.14-8.11 (dd, J = 2.7, 14.2, 1H), 7.66 (d. J = 8.5, 1H), 7.46 (ddd, J = 2.2, 2.2, 9.9, 1H), 7.24-7.21 (dd, J = 6.3, 8.2, 1H), 7.01-6.96 (ddd, J = 3.0, 8.6, 10.4, 1H), 6.94-6.90 (ddd, J = 2.8, 8.4, 8.4, 1H), 6.88 (d, J = 8.5, 1H), 6.12 (s, 1H), 6.03 (s, 1H), 5.59 (s, 1H), 2.27 (s, 3H), 2.12 (s, 3H), 1.34 (bs, 6H).

EXAMPLE 10

Preparation of 7,9-difluoro-5(*Z*)-(3-methyl-4-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **20**, Structure **2** of Scheme I, where R^9 = 3-methyl-4-pyridyl).

This compound was prepared in a similar fashion as that described in Example 1 from 3-methyl-4-picolyl lithium and Compound **11** (Structure **1** of Scheme I) as a yellow solid: ^{1}H-NMR (500 MHz, $CDCl_3$) 8.49 (d, J = 4.9, 1H), 8.39 (s, 1H), 8.19 (d, J = 5.5, 1H), 7.43 (d, J = 8.5, 1H), 7.17 (ddd, J = 9.5, 2.4, 2.1, 1H), 6.77 (ddd, J = 10.1, 8.5, 3.1, 1H), 6.73 (d, J = 8.5, 1H), 5.92 (s, 1H), 5.56 (s, 1H), 4.31 (bs, 1H), 2.24 (s, 3H), 2.12 (d, J = 1.2, 3H), 1.38 (bs, 6H).

EXAMPLE 11

Preparation of 7,9-difluoro-5(*Z*)-(2-methyl-3-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **21**, Structure **2** of Scheme I, where R^9 = 2-methyl-3-fluorophenyl).

This compound was prepared in a similar fashion as that described in Example 1 from 2-methyl-3-fluorobenzyl Grignard reagent and Compound **11** (Structure **1** of Scheme I) as a yellow solid: ^{1}H-NMR (400 MHz, Acetone-d_6) 8.06 (d, J = 7.8, 1H), 7.66 (d, J = 8.5, 1H), 7.47-7.43 (ddd, J = 2.2, 2.2, 9.9, 1H), 7.31-7.26 (dd, J = 7.9, 14.0, 1H), 7.01-6.93 (m, 2H), 6.87 (d, J = 8.5, 1H), 6.11 (bs, 1H), 6.02 (s, 1H), 5.59 (s, 1H), 2.20 (s, 3H), 2.13 (s, 3H), 1.33 (bs, 6H).

EXAMPLE 12

Preparation of 7,9-difluoro-5(*Z*)-(3-methyl-2-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **22**, Structure **2** of Scheme I, where R^9 = 3-methyl-2-pyridyl).

This compound was prepared in a similar fashion as that described in Example 1 from 3-methyl-2-picolyl lithium and Compound **11** (Structure **1** of Scheme I) as a yellow solid: ^{1}H-NMR (500 MHz, $CDCl_3$) 8.50 (dd, J = 4.6, 1.5, 1H), 7.50 (dd, J = 7.6, 1.5, 1H), 7.40 (d, J = 8.5, 1H), 7.15-7.12 (m, 1H), 7.07 (dd, J = 7.6, 4.6, 1H), 6.69 (d, J = 8.5, 1H), 6.66 (ddd, J = 10.2, 8.2, 2.7, 1H), 6.01 (s, 1H), 5.53 (d, J = 1.2, 1H), 4.26 (bs, 1H), 2.38 (s, 3H), 2.26 (d, J = 1.2, 3H), 1.33 (bs, 6H).

EXAMPLE 13

Preparation of 7,9-difluoro-5(*Z*)-(2,3-dimethylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **23**, Structure **2** of Scheme I, where R^9 = 2,3-dimethylphenyl).

This compound was prepared in a similar fashion as that described in Example 1 from 2,3-dimethylbenzyl Grignard reagent and Compound **11** (Structure **1** of Scheme I) as a yellow solid: ^{1}H-NMR (400 MHz, Acetone-d_6) 7.97 (d, J = 7.7, 1H), 7.63 (d, J = 8.5, 1H), 7.44-7.41 (ddd, J = 2.2, 2.2, 10.1, 1H), 7.16-7.13 (dd, J = 7.6, 7.6, 1H), 7.07 (d, J = 7.3, 1H), 6.94-6.89 (ddd, J = 2.9, 8.9, 11.0, 1H), 6.84 (d, J = 8.5, 1H), 6.07 (bs, 1H), 6.05 (s, 1H), 5.70 (s, 1H), 2.28 (s, 3H), 2.14 (s, 3H), 2.06 (s, 3H), 1.30 (bs, 6H).

EXAMPLE 14

Preparation of 7,9-difluoro-5(*Z*)-cyanomethylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **24**, Structure **2** of Scheme I, where R^9 = cyano).

This compound was prepared in a similar fashion as that described in Example 1 from acetonitrile lithium and Compound **11** (Structure **1** of Scheme I) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) 7.50 (d, J = 8.6, 1H), 7.24-7.19 (m, 1H), 6.87-6.81 (m, 1H), 6.83 (d, J = 8.6, 1H), 5.58 (s, 1H), 4.76 (s, 1H), 4.40 (s, 1H), 2.11 (d, J = 1.2, 3H), 1.57 (bs, 6H).

EXAMPLE 15

Preparation of 7,9-difluoro-5(*Z*)-hexylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **25**, Structure **2** of Scheme I, where R^9 = pentyl).

This compound was prepared in a similar fashion as that described in Example 1 from n-hexyl lithium and Compound **11** (Structure **1** of Scheme I) as a yellow solid: ^{1}H-NMR (500 MHz, $CDCl_3$) 7.32 (d, J = 8.2, 1H), 7.10 (ddd, J = 9.8, 2.7, 1.8, 1H), 6.69 (ddd, J = 10.4, 8.5, 2.7, 1H), 6.59 (d, J = 8.5, 1H), 5.49 (s, 1H), 4.86 (t, J = 7.9, 1H), 4.15 (bs, 1H), 2.35-2.27 (m, 2H), 2.08 (d, J = 1.2, 3H), 1.74-1.64 (m, 4H), 1.63-1.58 (m, 1H), 1.36-1.25 (m, 8H), 1.20-1.13 (m, 4H), 1.00-1.93 (m, 2H).

EXAMPLE 16

Preparation of 7,9-difluoro-5(*Z*)-(2-methoxy-5-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **26**, Structure **2** of Scheme I, where R^9 = 2-methoxy-5-fluorophenyl).

This compound was prepared in a similar fashion as that described in Example 1 from 2-methoxy-5-fluorobenzyl Grignard reagent and Compound **11** (Structure **1** of Scheme I) as a yellow solid: ^{1}H-NMR (400 MHz, Acetone-d_6) 8.15-8.12 (ddd, J = 1.6, 1.6, 10.6, 1H), 7.63 (d, J = 8.5, 1H), 7.46-7.43 (ddd, J = 2.2, 2.2, 10.2, 1H), 7.00-6.95 (m, 3H), 6.86-6.84 (d, J = 8.4, 1H), 6.27 (s, 1H), 6.06 (bs, 1H), 5.56 (s, 1H), 3.81 (s, 3H), 2.09 (s, 3H), 1.19 (bs, 6H).

EXAMPLE 17

Preparation of 7,9-difluoro-5(*Z*)-(2,4,5-trifluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **27**, Structure **2** of Scheme I, where R^9 = 2,4,5-trifluorophenyl).

This compound was prepared in a similar fashion as that described in Example 1 from 2,4,5-trifluorobenzyl Grignard reagent and Compound **11** (Structure **1** of Scheme I) as a yellow solid: ^{1}H-NMR (500 MHz, $CDCl_3$) 8.38-8.32 (m, 1H), 7.41 (d, J = 8.2, 1H), 7.18-7.16 (m, 1H), 6.93-6.87 (m, 1H), 6.79-6.75 (m, 1H), 6.69 (d, J = 8.2, 1H), 5.88 (s, 1H), 5.56 (s, 1H), 4.28 (bs, 1H), 2.08 (s, 3H), 1.34 (bs, 6H).

EXAMPLE 18

Preparation of 7,9-difluoro-5-methylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **28**, Structure **4** of Scheme I).

Treatment of Compound **11** (Structure 1 of Scheme I, where R^6 = methyl) with Tebbe reagent (0.5 M in toluene) afforded compound **28** as a yellow solid: ^{1}H-NMR (500 MHz, $CDCl_3$) 7.35 (d, J = 8.2, 1H), 7.13 (ddd, J = 9.8, 2.4, 2.1, 1H), 6.71 (ddd, J = 10.1, 8.5, 2.8, 1H), 6.65 (d, J = 8.2, 1H), 5.51 (d, J = 0.9, 1H), 5.19 (d, J = 1.5, 1H), 4.52 (d, J = 1.5, 1H), 4.20 (bs, 1H), 2.14 (d, J = 1.2, 3H), 1.30 (bs, 6H).

EXAMPLE 19

Preparation of 7,9-difluoro-5(*Z*)-bromomethylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **29**, Structure **5** of Scheme I).

Treatment of Compound **28** (Structure 4 of Scheme I) with NBS in DMF at rt for 10 min and standard work-up followed by chromatography provided compound **29** as a yellow foam: ^{1}H-NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.2, 1H), 7.15-7.11 (m, 1H),

6.75 (ddd, J = 10.1, 8.2, 2.7, 1H), 6.67 (d, J = 8.2, 1H), 5.54 (s, 1H), 5.53 (s, 1H), 4.24 (bs, 1H), 2.08 (d, J = 1.5, 3H), 1.30 (bs, 6H).

EXAMPLE 20

Preparation of 7,9-difluoro-5(*Z*)-(3-thienylmethylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **30**, Structure **2** of Scheme I, R^9 = 3-thiophene).

To a solution of compound **29** (Structure **5** of Scheme I) in DME was added $Pd(PPh_3)_4$ (3 mol%) and the mixture was stirred at rt for 15 min. A solution of 3-thiopheneboronic acid in DME and CsF were added to the reaction mixture. The reaction was heated at 80°C for 2 h, quenched with $NaHCO_3$ (sat'd aqueous) and extracted with EtOAc. Removal of solvent and chromatography of the crude mixture afforded **30** as yellow foam: ^{1}H-NMR (500 MHz, $CDCl_3$) 7.77 (d, J = 2.4, 1H), 7.54 (d, J = 4.0, 1H), 7.37 (d, J = 8.2, 1H), 7.32 (dd, J = 4.9, 3.1, 1H), 7.17-7.13 (m, 1H), 6.76-6.72 (m, 1H), 6.65 (d, J = 8.2, 1H), 5.76 (s, 1H), 5.54 (s, 1H), 4.23 (bs, 1H), 2.09 (d, J = 0.9, 3H), 1.34 (bs, 6H).

EXAMPLE 21

Preparation of 7,9-difluoro-5(*Z*)-(2-thienylmethylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **31**, Structure **2** of Scheme I, R^9 = 2-thiophene).

This compound was prepared in a similar fashion as that described in Example **20** from compound **29** (Structure **5** of Scheme I) and 2-thiopheneboronic acid as yellow foam: ^{1}H-NMR (500 MHz, $CDCl_3$) 7.39 (d, J = 8.5, 1H), 7.33 (d, J = 4.9, 1H), 7.23 (d, J = 3.7, 1H), 7.16-7.13 (m, 1H), 7.05 (dd, J = 5.2, 3.7, 1H), 6.78-6.74 (m, 1H), 6.65 (d, J = 8.2, 1H), 5.99 (s, 1H), 5.56 (s, 1H), 4.25 (bs, 1H), 2.09 (d, J = 0.9, 3H), 1.36 (bs, 6H).

EXAMPLE 22

Preparation of (±)-7,9-difluoro-5-methoxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **32**, Structure **6** of Scheme II).

Reduction of Compound **11** (Structure 1 of Scheme II) with DIBAL-H in toluene at –78°C for 1 h provided a lactal intermediate, which, upon treatment with TsOH in methanol, afforded Compound **32** as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) 7.39 (d, J = 8.6, 1H), 7.21 (dt, J = 8.8, 2.4, 1H), 6.75 (td, J = 9.3, 2.7, 1H), 6.60(d, J = 8.2, 1H), 6.40 (s, 1H), 5.53 (d, J = 1.5, 1H), 4.04 (s, 1H), 3.49 (s, 3H), 2.27 (d, J = 1.2, 3H), 1.34 (s, 3H), 1.20 (s, 3H).

EXAMPLE 23

Preparation of (±)-7,9-difluoro-5-phenyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **33**, Structure **7** of Scheme II, where R^8 = phenyl).

This compound was prepared by the following general procedure:

To a stirred solution of bromobenzene in THF at -78 °C under nitrogen atmosphere was added n-BuLi in hexanes (1.6 M). After one hour a solution of compound **11** (structure **1** of Scheme II) in THF was added dropwise and after 2 hours at -78 °C the temperature was allowed to rise to – 55 °C. The reaction mixture was stirred for an additional hour at this temperature, poured into an aqueous ammonium chloride solution and extracted twice with ethyl acetate. The organic extracts were washed with brine, combined, dried (Na_2SO_4), concentrated and purified using column chromatography on silica gel (heptanes/ ethyl acetate: gradient 20/1 to 10/1) to give structure 8 of Scheme II (R^8 = Phenyl) as an oil. This oil was dissolved in dichloromethane, and 0.2 mL of triethylsilane and 0.17 mL of boron trifluoride diethyl etherate were added. After stirring for 6 hours a saturated solution of sodium hydrogencarbonate was added and extracted three times with dichloromethane. The organic extracts were combined, dried (Na_2SO_4) and concentrated. Purification using HPLC (LUNA C18(2), CH_3CN/water, gradient 6/4 to 10/0) yielded compound **33** as a solid: ^1H NMR (400 MHz, DMF-d_7) 7.70 (d, J = 8.8, 1H), 7.40 (dq, J = 10, 1.8, 1H), 7.30 (M, 5H), 7.10 (s, 1H), 6.93 (d, J = 8.8, 1H), 6.92 (M, 1H), 6.54 (d, J = 1.6, 1H), 5.52 (t, J = 1.6, 1H), 2.30 (d, J = 1.2, 3H), 1.30 (s, 3H), 1.27 (s, 3H).

EXAMPLE 24

Preparation of (±)-7,9-difluoro-5-(3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **34**, Structure **7** of Scheme II, where R^8 = 3-methylbenzene).

Compound **34** was prepared in a similar fashion as that described in Example **23** from Compound **11** (Structure **1** of Scheme II) and 3-bromotoluene as a solid: ^{1}H NMR (400 MHz, DMF-d_7) 7.85 (d, J = 8.6, 1H), 7.56 (dq, J = 10, 1.8, 1H), 7.37 (t, J = 7.6, 1H), 7.30 (s, 1H), 7.25 (d, J = 7.8, 1H), 7.23 (s, 1H), 7.21 (d, J = 8, 1H), 7.09 (d, J = 8.8, 1H), 7.09 (M, 1H), 6.70 (s, 1H), 5.69 (t, J = 1.6, 1H), 2.41 (s, 3H), 2.21 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H).

EXAMPLE 25

Preparation of (±)-7,9-difluoro-5-(1,3-benzodioxol-5-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **35**, Structure **7** of Scheme II, where R^8 = 5-(1,3-benzodioxole)).

Compound **35** was prepared in a similar fashion as that described in Example 23 from Compound **11** (Structure **1** of Scheme II) and 5-bromo[1,3]benzodioxole as a solid: ^{1}H NMR (400 MHz, DMF-d_7) 7.85 (d, J = 8.6, 1H), 7.75 (dq, J = 10, 1.8, 1H), 7.16 (s, 1H), 7.10 (m, 1H), 7.08 d, J = 8.8, 1H), 7.04 (d, J = 1.6, 1H), 6.96 (d, J = 8.8, 1H), 6.8 (dd, J = 8.2, 1.8, 1H), 6.69 (d, J = 1.8, 1H), 6.21 (s, 2H), 5.68 (t, J = 1.6, 1H), 2.22 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H).

EXAMPLE 26

Preparation of (±)-7,9-difluoro-5-(4-bromophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **36**, Structure **7** of Scheme II, where R^8 = 4-bromobenzene).

Compound **36** was prepared in a similar fashion as that described in Example 23 from Compound **11** (Structure **1** of Scheme II) and 1,4-dibromobenzene as a solid: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.4, 1H), 7.33 (m, 2H), 7.1 (m, 2H), 6.99 (dq, J = 9.6, 2, 1H), 6.91 (s, 1H), 6.69 (d, J = 8.8, 1H), 6.56 (m, 1H), 5.48 (s, 1H), 4.06 (s, 1H), 1.97 (s, 1H), 1.30 (s, 3H), 1.26 (s, 3H).

EXAMPLE 27

Preparation of (±)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **37**, Structure **7** of Scheme II, where, R^8 = 4-chloro-3-methylbenzene).

Compound **37** was prepared in a similar fashion as that described in Example 23 from Compound **11** (Structure **1** of Scheme II) and 5-bromo-2-chlorotoluene as a solid: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.4, 1H), 7.15 (d, 8.8, 1H), 7.09 (d, J = 2, 1H), 6.98 (m, 2H), 6.90 (s, 1H), 6.70 (d, J = 8.8, 1H), 6.57 (m, 1H), 5.49 (s, 1H), 4.06 (s, 1H), 2.24 (s, 1H), 1.98 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H).

EXAMPLE 28

Preparation of (-)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (+)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **38** and **39**, Structure **7** of Scheme II, where R^8 = 4-chloro-3-methylbenzene).

These compounds were isolated as enantiomers of Compound **37** by a chiral HPLC separation. Retention times: OJ column 0.46 cm x 25 cm, flow 1ml/min, heptanes/ethanol 85/15; Rt = 12 min and 15 min. Compound **38** is the (-)-isomer: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.4, 1H), 7.15 (d, 8.8, 1H), 7.09 (d, J = 2, 1H), 6.98 (m, 2H), 6.90 (s, 1H), 6.70 (d, J = 8.8, 1H), 6.57 (m, 1H), 5.49 (s, 1H), 4.06 (s, 1H), 2.24 (s, 1H), 1.98 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H); Compound **39** is the (+)-isomer: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.4, 1H), 7.15 (d, 8.8, 1H), 7.09 (d, J = 2, 1H), 6.98 (m, 2H), 6.90 (s, 1H), 6.70 (d, J = 8.8, 1H), 6.57 (m, 1H), 5.49 (s, 1H), 4.06 (s, 1H), 2.24 (s, 1H), 1.98 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H).

EXAMPLE 29

Preparation of (±)-7,9-difluoro-5-(3-fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **40**, Structure **7** of Scheme II, where R^8 = 3-fluorobenzene).

Compound **40** was prepared in a similar fashion as that described in Example 23 from Compound **11** (Structure **1** of Scheme II) and 3-bromofluorobenzene as a solid: ^{1}H

NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.4, 1H), 7.18 (m, 1H), 7.05 (d, J = 8.2, 1H), 7.0 (dq, J = 10, 2, 1H), 6.95 (s, 1H), 6.89 (m, 2H), 6.70 (d, J = 8.6, 1H), 6.57 (m, 1H), 5.49 (d, J = 1.4, 1H), 4.06 (s, 1H), 1.99 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H).

EXAMPLE 30

Preparation of (±)-7,9-difluoro-5-(3-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **41**, Structure **7** of Scheme II, where R^8 = 3-chlorobenzene).

Compound **41** was prepared in a similar fashion as that described in Example 23 from Compound **11** (Structure **1** of Scheme II) and 3-bromochlorobenzene as a solid: ^{1}H NMR (500 MHz, *DMSO-d6*) 7.59 (d, J = 8.8, 1H), 7.36 (dq, J = 10.4, 1.8, 1H), 7.31 (m, 2H), 7.14 (s, 1H), 7.10 (m, 1H), 7.0 (s, 1H), 6.96 (m, 1H), 6.79 (d, J = 8.8, 1H), 6.57 (d, J = 2, 1H), 5.44 (t, J = 1.6, 1H), 1.90 (d, J = 1.4, 3H), 1.22 (s, 3H), 1.19 (s, 3H).

EXAMPLE 31

Preparation of (±)-7,9-difluoro-5-(3-bromophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **42**, Structure **7** of Scheme II, where R^8 = 3-bromobenzene).

Compound **42** was prepared in a similar fashion as that described in Example 23 from Compound **11** (Structure **1** of Scheme II) and 1,3-dibromobenzene as a solid: ^{1}H NMR (600 MHz, DMF-*d6*) 7.88 (d, J = 8.7, 1H), 7.67 (d, J = 8.4, 1H), 7.61 (s, 1H), 7.59

(dq, J = 10.2, 2.1, 1H), 7.50 (t, J = 7.8, 1H), 7.46 (d, J = 7.8, 1H), 7.30 (s, 1H), 7.13 (m, 1H), 7.11 (d, J = 8.7, 1H), 6.77 (s, 1H), 5.72 (s, 1H), 2.22 (s, 3H), 1.47 (s, 3H), 1.44 (s, 3H).

EXAMPLE 32

Preparation of (±)-7,9-difluoro-5-(4-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **43**, Structure **7** of Scheme II, where R^8 = 4-chlorobenzene).

Compound **43** was prepared in a similar fashion as that described in Example 23 from Compound **11** (Structure **1** of Scheme II) and 4-bromochlorobenzene as a solid: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.4, 1H), 7.17 (M, 4H), 6.99 (dq, J = 9.6, 2, 1H), 6.92 (s, 1H), 6.69 (d, J = 8.6, 1H), 6.56 (m, 1H), 5.48 (s, 1H), 4.45 (s, 1H), 1.97 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H).

EXAMPLE 33

Preparation of (±)-7,9-difluoro-1,2-dihydro-2,2,4,5-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **44**, Structure **7** of Scheme II, where R^8 = methyl).

Compound **44** was prepared in a similar fashion as that described in Example 23 from Compound **11** (Structure **1** of Scheme II) and methyllithium as a solid: ^{1}H NMR (500 MHz, DMF-d_7) 7.54 (d, J = 8.8, 1H), 7.41 (dq, J = 10, 2, 1H), 7.02 (m, 1H), 6.74

(d, J = 8.8, 1H), 6.36 (s, 1H), 6.16 (q, J = 6.4, 1H), 5.50 (m, 1H), 2.23 (s, 3H), 1.32 (d, J = 6.6, 3H), 1.21 (s, 3H), 1.16 (s, 3H).

EXAMPLE 34

Preparation of (±)-7,9-difluoro-5-(2-oxo-2-phenylethyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **45**, Structure **7** of Scheme II, where R^8 = 2-oxo-2-phenylethyl).

To a stirred solution of 0.31 mmol of compound **32** (Structure **6** of Scheme II) in 10 mL of dichloromethane and 0.3 mL of 1-phenyl-1-trimethylsilyloxyethene at -78 °C under a nitrogen atmosphere was added 0.22 mL of boron trifluoride diethyl etherate. After stirring for 30 minutes a saturated aqueous solution of sodium hydrogencarbonate was added and the resulting mixture was extracted three times with dichloromethane. The organic extracts were combined, dried (Na_2SO_4) and concentrated. Purification using column chromatography on silica gel (toluene) and then HPLC (LUNA C18(2), CH_3CN/water, gradient 95/5 to 100/0) yielded 50 mg of compound **45** as a solid: ^1H NMR (500 MHz, DMF-d_7) 7.91 (dd, J = 8.8, 1.2, 2H), 7.64 (d, J = 8.6, 1H), 7.64 (tt, J = 7.4, 1H), 7.50 (d, J = 8.4, 1H), 7.49 (m, 2H), 6.95 (m, 1H), 6.80 (dd, 1H), 6.82 (d, J = 8.4, 1H), 6.46 (d, J = 2, 1H), 5.55 (t, J = 1.8, 1H), 3.92 (dd, J = 17.4, 10, 1H), 3.02, (dd, J = 17.4, 2.4, 1H), 2.31, (s, 3H), 1.27 (s, 3H), 1.17 (s, 3H).

EXAMPLE 35

Preparation of (±)-7,9-difluoro-5-ethyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **46**, Structure **7** of Scheme II, where R^8 = ethyl).

Hydrogenation at atmospheric pressure of compound **47** in ethyl acetate using PtO_2 as catalyst and purification using HPLC (LUNA C18(2), CH_3CN/water) yielded compound **46** as a solid: ^{1}H NMR (500 MHz, DMF-d_7) 7.57 (d, J = 8.4, 1H), 7.43 (dq, J = 10.2, 1.8, 1H), 7.05 (m, 1H), 6.77 (d, J = 8.6, 1H), 6.39 (d, J = 1.6, 1H), 5.87 (dd, J = 10.2, 3.6, 1H), 5.54 (t, J = 1.8, 1H), 2.25 (d, J = 1.4, 3H), 1.74 (m, 1H), 1.52 (m, 1H), 1.27 (s, 3H), 1.18 (s, 3H), 1.00 (t, J = 7.4, 3H).

EXAMPLE 36

Preparation of (±)-7,9-difluoro-5-ethenyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **47**, Structure **7** of Scheme II, where R^8 = vinyl).

Compound **47** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and tributyl(ethenyl)tin as a solid: ^{1}H NMR (600 MHz, DMF-d_7) 7.78 (d, J = 8.7, 1H), 7.59 (dt, J = 10.2, 1H), 7.21 (m, 1H), 7.11 (d, J = 8.4, 1H), 6.67 (m, 1H), 6.61 (s, 1H), 6.23 (m, 1H), 5.72 (s, 1H), 5.45 (dt, J = 10.8, 1H), 5.15 (dt, J = 17.7, 1H), 2.41 (s, 3H), 1.43 (s, 6H).

EXAMPLE 37

Preparation of (±)-7,9-difluoro-5-(2-oxo-3-butenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **48**, Structure **7** of Scheme II, where R^8 = 2-oxo-3-butenyl).

Compound **48** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and 2-trimethylsilyloxy-1,3-butadiene as a solid: ^{1}H NMR (600 MHz, DMF-d_7) 7.61 (d, J = 8.7, 1H), 7.47 (dt, J = 10.5, 2.4, 1H), 7.02 (m, 1H), 6.80 (d, J = 8.7, 1H), 6.64 (dd, J = 10.5, 2.7, 1H), 6.45 (s, 1H), 6.40 (dd, J = 17.7, 11.1, 1H), 6.16 (d, J = 18, 1H), 5.91 (d, J = 11.4, 1H), 5.55 (s, 1H), 3.48 (dd, 1H), 2.62 (dd, J = 17.1, 2.7, 1H), 2.29 (s, 3H), 1.26 (s, 3H), 1.18 (s, 3H).

EXAMPLE 38

Preparation of Methyl (±)-7,9-difluoro-1,2-dihydro-α,α,2,2,4-pentamethyl-5*H*-chromeno[3,4-*f*]quinoline-5-ethanoate (Compound **49**, Structure **7** of Scheme II, whereR^8 = 1-methoxycarbonyl-1-methylethyl).

Compound **49** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and 1-methoxy-2-methyl-1-trimethylsilyloxypropene as a solid: ^{1}H NMR (600 MHz, DMF-d_7) 7.86 (d, J = 8.7, 1H), 7.64 (dt, J = 5.3, 1.8, 1H), 7.21 (m, 1H), 7.04 (d, J = 8.4, 1H), 6.80 (s, 1H), 6.48 (s, 1H), 5.73 (s, 1H), 3.81 (s, 3H), 2.49 (s, 3H), 1.57 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H), 1.10 (s, 3H).

EXAMPLE 39

Preparation of (±)-7,9-difluoro-5-ethynyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **50**, Structure **7** of Scheme II, where R^8 = acetylene).

Compound **50** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and ethynyltributyltin as a solid: ^{1}H NMR (400 MHz, DMF-d_7) 7.77 (d, J = 8.6, 1H), 7.66 (dt, J = 10, 1.6, 1H), 7.29 (m, 1H), 7.00 (d, J = 8.4, 1H), 6.86 (d, J = 2.2, 1H), 6.70 (s, 1H), 5.74 (s, 1H), 3.81 (dd, J = 2.4, 0.8, 1H), 2.59 (s, 3H), 1.49 (s, 3H), 1.37 (s, 3H).

EXAMPLE 40

Preparation of (±)-7,9-difluoro-5-cyano-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **51**, Structure **7** of Scheme II, where R^8 = cyano).

Compound **51** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and trimethylsilyl cyanide as a solid: ^{1}H NMR (400 MHz,DMF -d_7) 7.56 (d, J = 8.8, 1H), 7.46 (dq, J = 10,1.8, 1H), 7.1 (m, 1H), 7.04 (s, 1H), 6.79 (d, J = 8.8, 1H), 6.64 (s, 1H), 5.50 (q, 1H), 2.26 (s, 3H), 1.20 (s, 3H), 1.06 (s, 3H).

EXAMPLE 41

Preparation of (±)-7,9-difluoro-5-butyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **52**, Structure **7** of Scheme II, where R^8 = butyl).

Compound **52** was prepared in a similar fashion as that described in Example 23 from Compound **11** (Structure **1** of Scheme II) and n-butyllithium as a solid: ^{1}H NMR (600 MHz, DMF-d_7) 7.60 (d, J = 7.1, 1H), 7.46 (d, J = 7.1, 1H), 7.08 (m, 1H), 6.80 (d, J = 5.7, 1H), 6.42 (s, 1H), 5.98 (d, J = 7.1, 1H), 5.57 (s, 1H), 2.28 (s, 3H), 1.78 (m, 1H), 1.48 (m, 3H), 1.3 (m, 2H), 1.3 (s, 3H), 1.20 (s, 3H), 0.86 (t, J = 4.2, 3H).

EXAMPLE 42

Preparation of (±)-7,9-difluoro-5-(2-thienyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **53**, Structure **7** of Scheme II, where R^8 = 2-thiophene).

Compound **53** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and 2-(tributylstannyl)thiophene as a solid: ^{1}H NMR (600 MHz, DMF-d_7) 7.80 (d, J = 8.7, 1H), 7.53 (dd, J = 5.4, 1.2, 1H), 7.43 (d, J = 10.2, 1H), 7.26 (s, 1H), 6.96 (m, 1H), 6.93 (m, 1H), 6.91 (d, J = 8.7, 1H), 6.78 (d, J = 3.6, 1H), 6.52 (s, 1H), 5.57 (s, 1H), 2.14 (s, 3H), 1.27 (s, 6H).

EXAMPLE 43

Preparation of (±)-7,9-difluoro-5-(2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **54**, Structure **7** of Scheme II, where R^8 = 2-furyl).

Compound **54** was prepared in a similar fashion as that described in Example 23 from Compound **32** (Structure **6** of Scheme II) and 2-(tributylstannyl)furan as a solid: ^{1}H NMR (600 MHz, DMF-d_7) 7.69 (s, 1H), 7.65 (d, J = 8.7, 1H), 7.44 (dt, J = 11.4, 1H), 6.99 (s, 1H), 6.94 (m, 1H), 6.88 (d, 8.4, 1H), 6.48 (s, 1H), 6.30 (q, J = 1.5, 1H), 5.92 (d, J = 3.3, 1H), 5.49 (s, 1H), 2.10 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H).

EXAMPLE 44

Preparation of (±)-7,9-difluoro-5-allyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **55**, Structure **7** of Scheme II, where R^8 = allyl).

Compound **55** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and allyltrimethylsilane as a solid: ^{1}H NMR (400 MHz, DMF-d_7) 7.78 (d, J = 8.6, 1H), 7.64, (dq, J = 10.2, 1.8, 1H), 7.24 (m, 1H), 6.97 (d, J = 8.6, 1H), 6.61 (d, J = 1.6, 1H), 6.24 (dd, J = 10, 4, 1H), 6.09 (m, 1H), 6.73 (t, J = 1.6, 1H), 5.27 (m, 1H), 5.23 (m, 1H), 2.71 (m, 1H), 2.48 (m, 1H), 2.44 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H).

EXAMPLE 45

Preparation of (±)-7,9-difluoro-5-[3-(trifluoromethyl)phenyl]-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **56**, Structure **7** of Scheme II, where R^8 = 3-trifluoromethylphenyl).

Compound **56** was prepared in a similar fashion as that described in Example 23 from Compound **11** (Structure **1** of Scheme II) and 3-bromobenzotrifluoride as a solid: ^{1}H NMR (400 MHz, DMF-d_7) 7.87 (d, J = 8.6, 1H), 7.84 (m, 1H), 7.78 (t, J = 7.6, 2H), 7.72 (m, 1H), 7.57 (dq, J = 10, 1.8, 1H), 7.38 (s, 1H), 7.12 (m, 1H), 7.11 (d, J = 8.6, 1H), 6.78 (d, J = 2, 1H), 6.71 (t, J = 1.6, 1H), 2.21 (d, J = 1.4, 3H), 1.45 (s, 3H), 1.44 (s, 3H).

EXAMPLE 46

Preparation of Ethyl (±)-7,9-difluoro-1,2-dihydro-α-methylene-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline-5-propanoate (Compound **57**, Structure **7** of Scheme II, whereR^8 = 2-ethoxycarbonyl-2-propenyl).

Compound **57** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and ethyl 2-(trimethylsilylmethyl)acrylate as a solid: ^{1}H NMR (600 MHz, DMF-d_7) 7.52 (d, J = 8.7, 1H), 7.38 (dq, J = 10.2, 1.8, 1H), 6.94 (m, 1H), 6.69 (d, J = 8.4, 1H), 6.35 (d, J = 1.5, 1H), 6.17 (dd, J = 10.5, 4.2, 1H), 6.12 (d, J = 1.2, 1H), 5.45 (s, 1H), 5.40 (s, 1H), 4.12

(m, 2H), 2.57 (dd, J = 15, 10.5, 1H), 2.44 (dd, J = 15, 3.9, 1H), 2.23 (s, 3H), 1.21 (s, 3H), 1.18, (t, J = 7.2, 3H), 1.06 (s, 3H).

EXAMPLE 47

Preparation of (±)-7,9-difluoro-1,2-dihydro-β-methylene-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline-5-propanol (Compound **58**, Structure **7** of Scheme II, where R^8 = 2-hydroxymethyl-2-propenyl).

To a solution of 64 mg of compound **59** (Structure **7** of Scheme II, where R^8 = 2-acetyloxymethyl-2-propenyl) in 2 mL of methanol, 0.5 mL of THF and 0.5 mL of aqueous 20% KOH stirred at room temperature for 3 hours 2 M hydrochloric acid was added to adjust the pH to 7. A saturated solution of sodium hydrogencarbonate was added and the resulting mixture was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and concentrated to yield 60 mg of compound **58** as a solid: ^{1}H NMR (400 MHz, DMF-d_7) 7.46 (dd, J = 8.6, 1.8, 1H), 7.32 (dq, J = 10, 1.8, 1H), 6.90 (m, 1H), 6.65 (dd, J = 8.4, 1.8, 1H), 6.11 (d, J = 10.6, 1H), 5.40 (s, 1H), 4.98 (s, 1H), 4.66 (s, 1H), 4.20 (d, J = 14.2, 1H), 3.90 (d, J = 14.2, 1H), 2.36 (dd, J = 15.6, 10.8, 1H), 2.17 (s, 3.5H), 2.13 (s, 0.5H), 1.14 (s, 3H), 1.05 (s, 3H).

EXAMPLE 48

Preparation of (±)-7,9-difluoro-1,2-dihydro-β-methylene-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline-5-propanol acetate(Compound **59**, Structure **7** of Scheme II, where R^8 = 2-acetyloxymethyl-2-propenyl).

Compound **59** was prepared by a similar procedure as described in Example 34 from Compound **32** (Structure **6** of Scheme II) and ethyl 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate as a solid: ^{1}H NMR (600 MHz, DMF-d_7) 7.63 (d, J = 8.7, 1H), 7.49 (d, J = 9.9, 1H), 7.07 (m, 1H), 6.82 (d, J = 8.7, 1H), 6.45 (s, 1H), 6.26 (dd, J = 10.8, 2.7, 1H), 5.58 (s, 1H), 5.23 (s, 1H), 5.05 (s, 1H), 4.71 (d, J = 13.5, 1H), 4.60 (d, J = 13.5, 1H), 2.63 (dd, J = 16.2, 11.1, 1H), 2.35 (s, 1H), 2.32 (s, 3H), 2.08 (s, 3H), 1.29 (s, 3H), 1.22 (s, 3H).

EXAMPLE 49

Preparation of (±)-7,9-difluoro-5-(1-methylethenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **60**, Structure **7** of Scheme II, where R^8 = 1-methylvinyl).

Compound **60** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and (propen-2-yl)tributyltin as a solid: ^{1}H NMR (600 MHz, DMF-d_7) 7.76 (d, J = 8.3, 1H), 7.57 (dq, J = 10.2, 1.8, 1H), 7.21 (m, 1H), 7.02 (d, J = 8.7, 1H), 6.58 (s, 1H), 6.44 (s, 1H), 5.60 (m, 1H), 5.23 (s, 1H), 4.63 (s, 1H), 2.37 (s, 3H), 2.31 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H).

EXAMPLE 50

Preparation of (±)-7,9-difluoro-5-(N-methyl-2-pyrrolyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **61**, Structure **7** of Scheme II, where R^8 = N-methyl-2-pyrrolyl).

Compound **61** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and N-methyl-2-(tributylstannyl)pyrrole as a solid: ^{1}H NMR (400 MHz, DMF-d_7) 7.65 (dd, J = 8.6, 2, 1H), 7.43 (m, 1H), 7.05 (s, 1H), 6.92 (m, 1H), 6.89 (m, 1H), 6.81 (m, 1H), 6.43 (s, 1H), 5.74 (m, 1H), 5.48 (m, 1H), 5.42 (m, 1H), 3.95 (m, 3H), 1.98 (d, J = 2, 3H), 1.29 (d, J = 2.2, 3H), 1.21 (d, 3H).

EXAMPLE 51

Preparation of (±)-7,9-difluoro-5-phenylethynyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **62**, Structure **7** of Scheme II, where R^8 = phenylacetylene).

Compound **62** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and (phenylethynyl)tributyltin as a solid: ^{1}H NMR (400 MHz, DMF-d_7) 7.64 (dd, J = 8.6, 1H), 7.52 (m, 1H), 7.37 (m, 3H), 7.28 (m, 2H), 7.14 (m, 1H), 6.92 (d, J = 3, 1H), 6.86 (m, 1H), 6.76 (s, 1H), 5.60 (s, 1H), 2.49 (d, J = 1.8, 3H), 1.35 (d, J = 2, 3H), 1.22 (d, J = 2.2, 3H).

EXAMPLE 52

Preparation of (±)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **63**, Structure **7** of Scheme II, where R^8 = 2-benzo[b]thiophene).

Compound **63** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and 2-(tributylstannyl)benzo[b]thiophene as a solid: ^{1}H NMR (600 MHz, DMF-d_7) 8.11 (m, 1H), 7.94 (m, 1H), 7.89 (d, J = 8.7, 1H), 7.61 (dq, J = 9.9, 1H), 7.51 (m, 3H), 7.20 (s, 1H), 7.12 (m, 1H), 7.12 (d, J = 8.4, 1H), 6.75 (d, J = 1.5, 1H), 5.72 (s, 1H), 2.36 (d, J = 1.2, 3H), 1.48 (s, 3H), 1.45 (s, 3H).

EXAMPLE 53

Preparation of (-)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (+)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **64** and **65**, Structure **7** of Scheme II, where R^8 = 2-benzo[b]thiophene).

Compounds **64** and **65** were prepared by chiral HPLC separation of Compound **63** (Structure **7** of Scheme II, where R^8 = 2-benzothiophene) as pure enantiomers. Retention times: (R,R) Whelk-O2 10/100; 0.46 cm x 25 cm, flow 1ml/min, heptanes/iso-propanol 98/2; Rt = 14 min and 18 min. Compound **64** is the (-)-isomer; and compound **65** is the (+)-isomer.

EXAMPLE 54

Preparation of (±)-7,9-difluoro-5-(5-methyl-2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **66**, Structure **7** of Scheme II, where R^8 = 5-methyl-2-furyl).

Compound **66** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and 5-methyl-2-(tributylstannyl)furan as a solid: ^{1}H NMR (400 MHz, DMF-d_7) 7.82 (m, 1H), 7.62 (m, 1H), 7.12 (m, 2H), 7.05 (m, 1H), 6.65 (s, 1H), 6.07 (s, 1H), 5.92 (m, 1H), 5.67 (s, 1H), 2.41 (dd, J = 8.4, 3H), 2.22 (d, J = 8, 3H), 1.44 (m, 3H), 1.39 (m, 3H).

EXAMPLE 55

Preparation of (±)-7,9-difluoro-5-(2-benzo[b]furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **67**, Structure **7** of Scheme II, where R^8 = 2-benzo[b]furyl).

Compound **67** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and 2-(tributylstannyl)benzo[b]furan as a solid: ^{1}H NMR (400 MHz, $CDCl_3$) 7.49 (d, J = 8.6, 1H), 7.40 (d, J = 8.6, 1H), 7.36 (d, J = 8.4, 1H), 7.26 (m, 1H), 7.14 (m, 1H), 7.08 (m, 2H), 6.71 (d, J = 8.4, 1H), 6.58 (m, 1H), 6.23 (s, 1H), 5.48 (d, J = 1.4, 1H), 4.05 (s, 1H), 2.04 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H).

EXAMPLE 56

Preparation of (±)-7,9-difluoro-5-[4-(dimethylamino)phenyl]-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **68**, Structure **7** of Scheme II, where R^8 = 4-dimethylaminophenyl).

Compound **68** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and (3-[dimethylamino]phenyl)tributyltin as a solid: ^{1}H NMR (400 MHz, DMSO-d_6) 7.54 (d, J = 8.8, 1H), 7.32 (dq, J = 10.2, 1H), 6.92 (m, 2H), 6.88 (m, 1H), 6.85 (s, 1H), 6.74 (d, J = 8.6, 1H), 6.54 (m, 2H), 6.43 (d, J = 1.8, 1H), 5.38 (s, 1H), 2.82 (s, 6H), 1.90 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H).

EXAMPLE 57

Preparation of (±)-7,9-difluoro-5-(5-methyl-2-thienyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **69**, Structure **7** of Scheme II, where R^8 = 5-methyl-2-thiophene).

Compound **69** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and 5-methyl-2-(tributylstannyl)thiophene as a solid: ^{1}H NMR (400 MHz, DMSO-d_6) 7.55 (d, J = 8.6, 1H), 7.36 (dq, J = 10.2, 1.8, 1H), 7.05 (s, 1H), 6.96 (m, 1H), 6.75 (d, J = 3.4, 1H), 6.52 (dd, J = 3.8, 1.2, 1H), 6.48 (d, J = 2, 1H), 6.40 (d, J = 3.4, 1H), 5.41 (s, 1H), 2.11 (s, 3H), 2.01 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H).

EXAMPLE 58

Preparation of (±)-7,9-difluoro-5-(5-methoxy-2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **70**, Structure **7** of Scheme II, where R^8 = 5-methoxy-2-furyl).

Compound **70** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and 5-methoxy-2-(tributylstannyl)furan as a solid: ^{1}H NMR (600 MHz, $CDCl_3$) 7.35 (d, J = 8.7, 1H), 7.06 (dt, J = 9.6, 1H), 6.80 (s, 1H), 6.65 (d, J = 8.4, 1H), 6.62 (m, 1H), 5.69 (d, J = 3.3, 1H), 5.47 (s, 1H), 4.88 (d, J = 3.3, 1H), 3.98 (s, 1H), 3.79 (s, 3H), 2.05 (d, J = 0.9, 3H), 1.29 (s, 3H), 1.22 (s, 3H).

EXAMPLE 59

Preparation of (±)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **71**, Structure **7** of Scheme II, where R^8 = 2-propynyl).

Compound **71** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and 2-propynyltributyltin as a solid: ^{1}H NMR (400 MHz, DMF-d_7) 7.57 (d, J = 8.8, 1H), 7.43 (dq, J = 10.4, 1.8, 1H), 7.05 (m, 1H), 6.77 (d, J = 8.6, 1H), 6.44 (s, 1H), 6.19 (q, J = 4.6, 1H), 5.51 (t, J = 1.8, 1H), 2.84 (t, J = 2.8, 1H), 2.64 (m, 1H), 2.48 (dq, J = 17.6, 2.8, 1H), 2.27 (s, 3H), 1.25 (s, 3H), 1.16 (s, 3H).

EXAMPLE 60

Preparation of (-)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (+)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **72** and **73**, Structure **7** of Scheme II, where R^8 = 2-propynyl).

Compounds **72** and **73** were prepared by chiral HPLC separation of Compound **71** (Structure **7** of Scheme II, where R^8 = 2-propynyl) as pure enantiomers. Retention times: OJ column 2.0 cm x 50 cm, flow 10 ml/min, heptanes/ethanol 90/10; Rt = 40 min and 45 min. Compound **72** is the (-)-isomer; and Compound **73** is the (+)-isomer.

EXAMPLE 61

Preparation of (±)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **74**, Structure **7** of Scheme II, where R^8 = 1-propynyl).

Compound **74** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and (1-propynyl)tributyltin as a solid: ^{1}H NMR (400 MHz, DMSO-d_6) 7.46 (d, J = 8.6, 1H), 7.42 (dq, J = 10,1.8, 1H), 7.08 (m, 1H), 6.67 (d, J = 8.6, 1H), 6.54 (q, J = 2.2, 1H), 6.48 (d, J = 2, 1H), 5.46 (t, J = 1.6, 1H), 2.29 (s, 3H), 1.69 (d, J = 2, 3H), 1.25 (s, 3H), 1.11 (s, 3H).

EXAMPLE 62

Preparation of (-)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (+)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **75** and **76**, Structure **7** of Scheme II, where R^8 = 1-propynyl).

Compounds **75** and **76** were prepared by chiral HPLC separation of Compound **74** (Structure **7** of Scheme II, where R^8 = 1-propynyl) as pure enantiomers. Retention times: OJ column 2.0 cm x 50 cm, flow 10 ml/min, heptanes/ethanol 90/10; Rt = 37 min and 47 min. Compound **75** is the (-)-isomer; and Compound **76** is the (+)-isomer.

EXAMPLE 63

Preparation of (±)-7,9-difluoro-5-(4,5-dimethyl-2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **77**, Structure **7** of Scheme II, where R^8 = 4,5-dimethyl-2-furyl).

Compound **77** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and 2,3-dimethyl-5-(tributylstannyl)furan as a solid: ^{1}H NMR (400 MHz, DMSO-d_6) 7.54 (d, J = 8.6, 1H), 7.39 (dq, J = 10, 1.8, 1H), 6.97 (m, 1H), 6.80 (s, 1H), 6.74 (d, J = 8.4, 1H), 6.46 (d, J = 1.8, 1H), 5.55 (s, 1H), 5.40 (s, 1H), 2.12 (s, 3H), 1.92 (s, 3H), 1.69 (s, 3H), 1.21 (s, 3H), 1.13 (s, 3H).

EXAMPLE 64

Preparation of (±)-7,9-difluoro-5-(2-methyl-1-propenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **78**, Structure **7** of Scheme II, where R^8 = 2-methyl-1-propenyl).

Compound **78** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and 2-methylpropenylmagnesium bromide as a solid: ^{1}H NMR (400 MHz, DMSO-d_6) 7.47 (d, J = 8.6, 1H), 7.36 (m, 1H), 6.98 (m, 1H), 6.66 (d, J = 8.4, 1H), 6.41 (d, J = 1.8, 1H), 6.38 (d, J = 7.4, 1H), 5.42 (s, 1H), 5.17 (d, J = 7.6, 1H), 2.11 (s, 3H), 1.88 (s, 3H), 1.62 (s, 3H), 1.21 (s, 3H), 1.14 (s, 3H).

EXAMPLE 65

Preparation of (±)-7,9-difluoro-5-(3,4-dimethyl-2-thiennyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **79**, Structure **7** of Scheme II, where R^8 = 3,4-dimethyl-2-thiophene).

Compound **79** was prepared in a similar fashion as that described in Example 34 from Compound **32** (Structure **6** of Scheme II) and 3,4-dimethyl-2-(tributylstannyl)thiophene as a solid: ^{1}H NMR (600 MHz, DMSO-d_6) 7.55 (d, J = 9, 1H), 7.38 (m, 1H), 7.12 (s, 1H), 6.91 (m, 1H), 6.87 (s, 1H), 6.76 (d, J = 8.4, 1H), 6.46 (d, J = 1.8, 1H), 5.38 (s, 1H), 2.27 (s, 3H), 2.05 (s, 3H), 1.93 (s, 3H), 1.18 (s, 3H), 1.16 (s, 3H).

EXAMPLE 66

Preparation of (±)-7,9-difluoro-5-(3-(3-bromophenyl)phenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **80**, Structure **7** of Scheme II, where R^8 = 3-(3-bromophenyl)phenyl).

Compound **80** was isolated as a minor product of the reaction described in example 31 as a solid: ^{1}H NMR (600 MHz, DMSO-d_6) 7.65 (t, J = 2.1,1H), 7.58 (d, J = 8.7, 1H), 7.55 (m, 1H), 7.49 (m, 1H), 7.41 (t, J = 8.4, 1H), 7.35 (m, 2H), 7.09 (d, J = 7.8, 1H), 7.08 (s, 1H), 6.93 (m, 1H), 6.79 (d, J = 8.7, 1H), 6.53 (d, J = 2.1, 1H), 5.45 (s, 1H), 1.97 (s, 3H), 1.21 (s, 6H).

EXAMPLE 67

Preparation of 7,9-difluoro-5(*Z*)-(2-methylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **81**, Structure **2** of Scheme I, where R^9 = 2-methylphenyl).

This compound was prepared in a similar fashion as that described in Example 1 from 2-methylbenzyl Grignard reagent and Compound **11** (Structure **1** of Scheme I) as a yellow solid: ^{1}H-NMR (400 MHz, $CDCl_3$) 8.30 (d, J = 8.0, 1H), 7.38 (d, J = 8.4, 1H), 7.31-7.24 (m, 1H), 7.17-7.10 (m, 4H), 6.73-6.82 (m, 1H), 6.66 (d, J = 8.4, 1H), 5.96 (s, 1H), 5.53 (s, 1H), 4.24 (s, 1H), 2.28 (s, 3H), 2.14 (s, 3H), and 1.25 (bs, 6H).

EXAMPLE 68

The PR modulating activities and binding affinities of selected steroid receptor modulator compounds of the present invention were evaluated utilizing the cotransfection assay, and the standard receptor competitive binding assays, according to the following illustrative Examples. The receptor-selectivities of the selected analogues towards PR relative to other steroid hormone receptors were also assessed in

the cotransfection assay under the same cell background. The potential tissue-selectivities of the selected analogues were examined by using the T47D alkaline phosphatase assay that was developed from human breast cancer cells with endogenous PRs.

Cotransfection assay

The function and detailed preparation procedure of the cotransfection assays have been described previously (Pathirana, C. *et al.*, Nonsteroidal Human Progesterone Receptor Modulators from the Marine Alga Cymopolia Barbata. *Mol. Pharm.* **1995**, *47*, 630-635). Briefly, the cotransfection assays were carried out in CV-1 cells (African green monkey kidney fibroblasts), which were transiently transfected, by the standard calcium phosphate coprecipitation procedure (Berger, T. S. *et al.*, Interaction of Glucocorticoid Analogues with the Human Glucocorticoid Receptor. *J. Steroid Biochem. Mol. Bio.* **1992**, *41*, 733-738) with the Plasmid containing receptor, MTV-LUC reporter, pRS-β-Gal, and filler DNA (Rous sarcoma virus chloramphenicol acetyltransferase). The agonist activity was determined by examining the LUC expression (normalized response) and the efficacy readout was a relative value to the maximal LUC expression produced by a reference agonist as 100%, *e.g.*, progesterone for hPR, dihydrotestosterone (DHT) for human androgen receptor (hAR), dexamethasone for hGR, aldosterone for human mineralocorticoid receptor (hMR) and estradiol for human estrogen receptor (hER). Antagonist efficacy was determined as a function (%) of maximal inhibition of a reference agonist at EC_{50} concentration. All the

cotransfection experiments were carried out in 96-well plates by automation (Beckman Biomomek automated workstation).

Receptor Binding Assays

The preparation of receptor binding assays for hPR-A was described in literature (Pathirana, C. *et al.*, Nonsteroidal Human Progesterone Receptor Modulators from the Marie Alga Cymopolia Barbata. *Mol. Pharm.* **1995**, *47*, 630-635.)

T47D Alkaline Phosphatase Assay

The T47D alkaline phosphatase assays were performed as described previously (Lorenzo, D. D. et. Al., Progestin Regulation of Alkaline phosphatase in the Human Breast Cancer Cell Line T47D. *Cancer Res.* **1991**, *51*, 4470).

The agonist, antagonist and binding activity assay results of selected progesterone receptor modulator compounds of the present invention and the standard reference compounds on PR are shown in Table 1 below. Efficacy is reported as the percent maximal response observed for each compound relative to the reference agonist and antagonist compounds indicated above. Also reported in Table 1 for each compound is its antagonist potency or IC_{50} (which is the concentration (nM), required to reduce the maximal response by 50%), and its agonist potency or EC_{50} (nM), (which is the effective concentration that produced 50% of the maximum response). Table 1 also lists the PR modulating activity in T47D cells to assess the potential tissue-selectivity comparing to marketed steroidal progestins or antiprogestins. All of the reference

steroids demonstrated full agonist or antagonist activties in both cell lines; however, the 7,9-difluoro compounds of the subject invention behaved as partial agonist/antagonist activities in human breast cancer cell line despite the full agonist or antagonist activities in the CV-1 cells.

Table 1: Agonist, antagonist and binding activity of progesterone receptor modulator compounds of present invention and the reference agonist compounds and reference antagonists compounds.

Cmpd	hPR Agonist CV-1 Cells		hPR Antagonist CV-1 Cells		hPR AgonistT47D cells		hPR Antagonists T47D Cells		PR binding
No.	Eff. (%)	EC_{50} (nM)	Eff. (%)	IC_{50} (nM)	Eff. (%)	EC_{50} (nM)	Eff. (%)	IC_{50} (nM)	K_i (nM)
Prog.	100	0.5	na	na	100	2.3	na	na	3.5
MPA	88	0.4	na	na	114	0.7	na	na	1.4
Norethindrone	170	1.2	na	na	103	0.7	na	na	1.2
Levonorgestrel	216	0.1	na	na	96	0.5	na	na	0.4
Drospirenone	87	2.2	na	na	117	6.0	na	na	12
3-ketodesogestrel	190	0.1	na	na	94	0.2	na	na	0.3
RU486	na	na	94	0.6	na	na	94	3.7	1.1
ZK299	na	na	99	1.6	na	na	86	2.8	18
10	153	4.9	na	na	54	30	49	97	6.8
14	103	7.4	na	na	58	49	44	116	6.0
15	191	3.8	na	na	56	19	52	711	9.7
17	169	2.9	na	na	62	12	42	389	9.5
18	142	1.3	na	na	57	17	58	55	3.9
19	212	1.4	na	na	65	8.7	35	360	8.5
20	147	2.8	na	na	63	6.6	59	170	2.9
24	52	9.4	na	na	72	79	26	830	58
26	159	0.6	na	na	63	7.5	46	610	9.0
29	191	2.3	na	na	62	8.7	40	170	7.0
30	186	5.3	na	na	66	33	44	840	4.5
31	171	2.7	na	na	66	14	39	610	7.9
32	na	na	76	75	36	315	35	250	37
33	85	3.5	na	na	62	35	na	na	2.7
34	114	1.2	na	na	60	34	47	565	2.5
37	89	1.24	na	na	50	130	56	150	2.2
38	110	1.2	na	na	54	6.2	nt	nt	2.0
39	26	28	62	24	na	na	29	4100	nt
41	146	1.87	na	na	54	42	50	135	2.8
45	na	na	79	42	77	195	na	na	18

Cmpd	hPR Agonist CV-1 Cells		hPR Antagonist CV-1 Cells		hPR AgonistT47D cells		hPR Antagonists T47D Cells		PR binding
No.	Eff. (%)	EC_{50} (nM)	Eff. (%)	IC_{50} (nM)	Eff. (%)	EC_{50} (nM)	Eff. (%)	IC_{50} (nM)	K_i (nM)
63	154	2.3	na	na	61	20	49	490	6.5
74	89	0.7	na	na	58	4.6	40	53	3.5

na = not active (*i.e.* efficacy of <20 and potency of >10,000)
nt = not tested

The receptor-selectivity profile of selected analogues was examined in the cotransfection assays with different steroid hormone receptors in comparison with the steroidal reference compounds and Table 2 lists the receptor-selectivity potency ratio of selected 7,9-difluoro analogues and PR modulating steroids. In general, the nonsteroidal analogues demonstrated more selectivity towards hPR than the steroids.

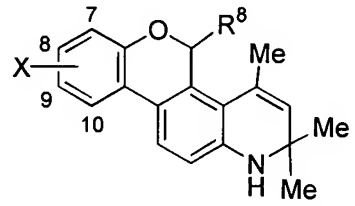
Table 2: Progesterone receptor-selectivity of selective PR modulator compounds of present invention and the reference steroidal progestins.

Cmpd	hAR EC_{50} or IC_{50}/ hPR EC_{50}	hGR EC_{50} or IC_{50}/ hPR EC_{50}	hMR EC_{50} or IC_{50} / hPR EC_{50}	hER EC_{50} or IC_{50}/ hPR EC_{50}
Prog	23	>1000	25	>1000
MPA	41	67	>1000	>1000
Noret hindrone	33	34	>1000	9
Levonorgestrel	>1000	142	>1000	>1000
3-ketodesogestrel	>1000	896	>1000	>1000
10	320	290	>1000	>1000
14	54	365	>1000	>1000
15	2	30	>1000	>1000
17	622	66	>1000	>1000
18	170	77	>1000	>1000
19	>1000	432	>1000	>1000
20	8	27	>1000	>1000
26	742	342	>1000	>1000
29	6	83	>1000	>1000
30	377	19	>1000	>1000
31	517	59	>1000	>1000
33	37	10	>1000	>1000
34	8.5	>1000	>1000	>1000
37	558	54	>1000	>1000
41	252	105	905	>1000
63	136	8.8	>1000	685
74	100	>1000	>1000	>1000

EXAMPLE 69

The 7,9-difluoro substituents at the D-ring of formulae I and II of the present invention are generally superior to any other substituents in modulating PR activities, which is unexpected and surprising, in view of U.S. Patent Nos. 5,693,646 and 5,696,127. The superiority of the 7,9-difluoro analogue compounds of the present invention was demonstrated utilizing the hPR cotransfection assay according to the following illustrative Examples. The EC_{50} comparison between the new 7,9-difluoro compounds and analogues with substitution patterns different from 7,9-difluoro (disclosed in U.S. Patent Nos. 5,693,646 and 5,696,127) are tabulated in Tables 3 and 4.

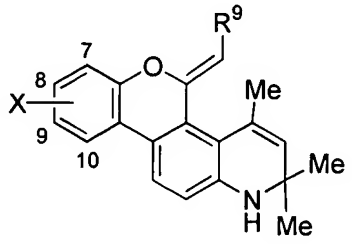
Table 3: hPR agonist potencies (EC_{50} in nM) of selected 7,9-difluoro compounds of present invention (Formula I) and analogues with other D-ring substitution patterns in the cotransfection assay.



X →	7,9-diF		H	9-F	9-OMe	9-Cl	9-Me	8-F
R^8	#	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}
Ph	33	3.5	203[a]	7.4[b]	-[c]	6.9[b]	-	-
3-F-Ph	40	6.66	9[a]	-	-	3.7[b]	-	-
3-Cl-Ph	41	1.87	18[b]	2.8[b]	-	3.6[b]	4.85	-
4-Cl-Ph	43	5.1	15[b]	8.1[b]	3.1[b]	9[b]	-	10[b]
3-Br-Ph	42	3.65	8[b]	-	-	-	-	-
4-Br-Ph	36	4.96	14[b]	-	-	5.2[b]	-	-
3-Me-Ph	34	1.2	145	5.0[b]	11	7.1[b]	44	-
3-CF_3-Ph	56	1.6	13[a]	10[b]	-	7.4	-	-
4-Cl-3-Me-Ph	37	1.24	14[b]	2.7[b]	-	9.4	7.45	-
Benzodioxol-5-yl	35	3.85	48	-	-	-	-	-
Me	44	1.4	2067	13	-	3	-	-
Et	46	6.93	-	9	-	-	-	-
Allyl	55	3.6	839	7.5	-	-	-	-
Bu	52	15	16[a]	16[a]	9	7	16	5285

[a] EC_{50} data from U.S. Pats 5693646/5693647/5696127;
[b] EC_{50} data from *J. Med. Chem.* 41 (1998), 291 and 303;
[c] "-" means compound not prepared.

Table 4: hPR agonist potencies (EC_{50} in nM) of selected 7,9-difluoro compounds of present invention (Formula II) and analogues with other D-ring substitution patterns in the cotransfection assay.



X →	7,9-diF		H	9-F	8-OH	9-OH	8-OMe	9-OMe	7-Cl	9-Cl	9-Me	8-F	8,9-diF
R^9	**#**	**EC_{50}**	**EC_{50}**	**EC_{50}**	**EC_{50}**	**EC_{50}**	**EC_{50}**	**EC_{50}**	**EC_{50}**	**EC_{50}**	**EC_{50}**	**EC_{50}**	**EC_{50}**
Phenyl	**10**	**4.9**	**33**[a]	**5.25**	-[c]	**54.4**	**5.5**	**67**	**6.2**	**6.24**	-	**187**	-
2-F-Ph	**12**	**2.55**	**29**[b]	**7.3**	-	-	**45**	-	-	**26.5**	-	-	-
3-F-Ph	**15**	**3.8**	**7.6**[b]	**7**	-	**5.75**	**8.6**	-	-	**11.6**	**7.95**	**109**	-
4-F-Ph	**16**	**3.7**	**59.5**[b]	**3.95**	-	-	-	-	-	-	-	-	-
2-Cl-Ph	**13**	**1.92**	**57.8**[b]	**12**	-	-	**>1000**	-	-	-	-	-	-
2,5-diF-Ph	**17**	**2.9**	**14.7**[b]	**3**	**10**	**10**	-	-	-	**25**	-	-	-
2-Me-3-F-Ph	**21**	**8.2**	-	**8.4**	-	-	-	-	-	-	-	-	-
2-Me-5-F-Ph	**19**	**1.4**	**2.6**	**2.1**	-	-	-	-	-	**2.1**	-	-	**3.95**
2-MeO-5-F-Ph	**26**	**0.6**	-	**0.9**	-	**11.5**	-	-	-	-	-	-	-
2-MeO-Ph	**18**	**1.3**	-	**0.93**	-	-	**24.0**	-	-	-	-	-	-
2-Me-Ph	**81**	**1.66**	**5.7**[b]	**4**[a]	-	**9.3**	**3.5**	**67.5**	-	**8.5**	-	**13**	**13**
4-pyridinyl	**14**	**7.4**	-	**5.8**	-	-	**36**	-	-	-	-	-	-
3-Me-4-pyridinyl	**20**	**2.8**	-	**2.0**	-	-	**24**	-	-	-	-	-	-
2-Thienyl	**31**	**2.7**	-	**18**	-	-	-	-	-	-	-	-	-

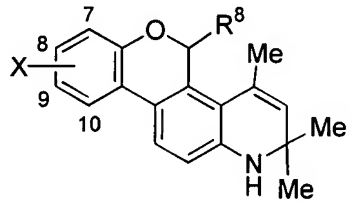
[a] EC_{50} data from U.S. Pats 5693646/5693647/5696127;
[b] EC_{50} data from *J. Med. Chem.* 41 (1998), 291 and 303;
[c] "-" means compound not prepared.

EXAMPLE 70

The 7,9-difluoro substituents at the D-ring of formulae I and II of the present invention are generally superior to any other substituents in tissue-selectivity, which is unexpected and surprising, in view of U.S. Patent Nos. 5,693,646 and 5,696,127. The superiority of the 7,9-difluoro analogue compounds of the present invention was further characterized utilizing a multi-endpoint adult rat model according to the following illustrative Examples. In this assay, advantage is taken of the fact that in the uterus, estrogens induce a proliferation and increase in the epithelial cell height and uterine wet weight, which can be antagonized by progestins. In the breast, estrogens induce a proliferation of the ductal network while progestins stimulate the growth of the lobular-alveolar end buds, which grow from the distal end of the ducts. The assay is carried out in ovariectomized female rats by treating them for three days with estrone or estrone plus varying doses of a progestin; in this case MPA was used. Proliferating cells or inhibition of proliferating cells were quantitated either by measurements of cell height in sectioned and stained tissue samples or, in the case of the breast, immuno-histochemically labeled Brdu incorporated nuclei. The tissue-selectivity comparison between the new 7,9-difluoro compounds and analogues with substitution patterns different from 7,9-difluoro (disclosed in U.S. Patent Nos. 5,693,646 and 5,696,127) are tabulated in Tables 5 and 6. The uterus/breast tissue-selectivity is presented as the ratio

of relative efficacy to MPA in uterus verse in breast tissue at the same highest dose tested.

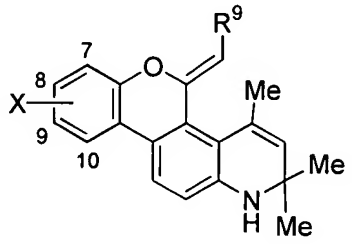
Table 5: The uterus/breast tissue-selectivity of selected 7,9-difluoro compounds of present invention (Formula I) and analogues with other D-ring substitution patterns in an adult rat model.



X →	7,9-diF		H	9-F
R^8	Compd #	selectivity	selectivity	selectivity
Ph	33	-[a]	0.78	-
n-butyl	52	-	-	2.0
2-benzo-thiophene	64	2.8	-	-
4-Cl-3-Me-Ph	38	2.8	-	-
1-propynyl	75	4.2	-	-
4-Cl-Ph	43	-	1.5	-
3-CF_3-Ph	56	-	3.5	-

[a] "-" means compound not tested in the assay.

Table 6: The uterus/breast tissue-selectivity of selected 7,9-difluoro compounds of present invention (Formula II) and analogues with other D-ring substitution patterns in an adult rat model.



X →	7,9-diF		H	9-F
R^8	Compd #	selectivity	selectivity	selectivity
2,5-diF-Ph	17	2.7	-[a]	-
3-F-Ph	15	-	0.69	2.2
2-thienyl	31	3.5	-	-
2-Me-5-F-Ph	19	3.5	-	
2-Me-Ph	81	-	-	2.3

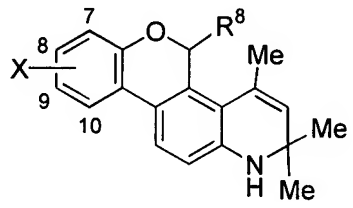
[a] "-" means compound not tested in the assay.

EXAMPLE 71

The 7,9-difluoro substituents at the D-ring of formulae I and II of the present invention are generally superior to any other substituents in PR agonist activity *in vivo*, which is unexpected and surprising, in view of U.S. Patent Nos. 5,693,646 and 5,696,127. The superiority of the 7,9-difluoro analogue compounds of the present invention was further characterized utilizing the McPhail rabbit model according to the following illustrative Examples. The Clauberg or McPhail assay is a classic assay utilizing rabbits to measure progestational activity. The reason rabbit is used is because the results observed in rabbit have proved to be a good indicator and predictor of

activity in the human. In this assay, immature rabbits are treated initially with estradiol, which induces growth in the uterus. This is followed by a progestin, which causes a large change in the glandular content of the uterus. It is this change in the glandular component which is a measure of the progestational activity of a progestin. The measurement of these glandular changes is carried out histologically using stained sections of the uterus. The *in vivo* comparison between the new 7,9-difluoro compounds and analogues with substitution patterns different from 7,9-difluoro (U.S. Patent Nos. 5,693,646 and 5,696,127) is tabulated in Tables 7 and 8. The *in vivo* potency of the progestins is presented as the minimum active dose (MAD).

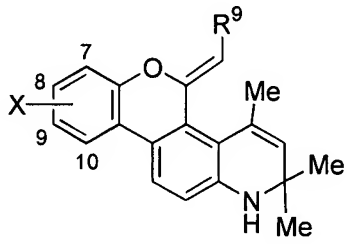
Table 7: The potency (MAD in mg/kg) of selected 7,9-difluoro compounds of present invention (Formula I) and analogues with other D-ring substitution patterns in the McPhail assay.



X →	7,9-diF		7-F	9-F	9-Me
R^8	Compd #	MAD	MAD	MAD	MAD
3-F-Ph	40	-[a]	-	-	>2
3-Me-Ph	34	1.0	-	-	-
2-benzo-thiophene	64	0.25	-	-	-
4-Cl-3-Me-Ph	38	0.25	0.5	1.0	-
1-propynyl	75	<0.5	-	-	-
2-propynyl	71	<0.5	-	-	-
3-Cl-Ph	41	0.75	-	-	-

[a] "-" means compound not tested in the assay.

Table 8: The potency (MAD in mg/kg) of selected 7,9-difluoro compounds of present invention (Formula II) and analogues with other D-ring substitution patterns in the McPhail assay.



X →	7,9-diF		7-F	9-F
R^8	Compd #	MAD	MAD	MAD
2,5-diF-Ph	17	0.25	0.5	-[a]
2-F-Ph	12	0.5	-	-
3-F-Ph	15	0.18	-	-
2-MeO-Ph	18	2.0	-	-
2-Me-5-F-Ph	19	0.1	1.0	-
2-MeO-5-F-Ph	26	2.0	-	-
2-Me-Ph	81	-	-	1.2
3-Me-pyridine-4-	20	0.25	-	-

[a] "-" means compound not tested in the assay.

Pharmacological and Other Applications

The following Example provides illustrative pharmaceutical composition formulations:

EXAMPLE 72

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
COMPOUND **10**	10
Starch, dried	200
Magnesium stearate	10
Total	220 mg

The above ingredients are mixed and filled into hard gelatin capsules in 220 mg quantities.

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
COMPOUND **10**	10
Cellulose, microcrystalline	200
Silicon dioxide, fumed	10
Stearic acid	10
Total	230 mg

The components are blended and compressed to form tablets each weighing 230 mg.

Tablets, each containing 10 mg of active ingredient, are made as follows:

	Quantity (mg/tablet)
COMPOUND **10**	10
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (PVP) (as 10% solution in water)	4

Sodium carboxymethyl starch (SCMS)	4.5
Magnesium stearate	0.5
Talc	1.0
Total	100 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of PVP is mixed with the resultant powders, which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The SCMS, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Suppositories, each containing 225 mg of active ingredient, may be made as follows:

	Quantity (mg/suppository)
COMPOUND **10**	20
Saturated fatty acid glycerides	2,000
Total	2,020 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of normal 2 g capacity and allowed to cool.

An intravenous formulation may be prepared as follows:

	Quantity
COMPOUND **10**	10 mg
isotonic saline	1000 mL
glycerol	100 mL

The compound is dissolved in the glycerol and then the solution is slowly diluted with isotonic saline. The solution of the above ingredients is then administered intravenously at a rate of 1 mL per minute to a patient.

The present invention includes any combination of the various species and subgeneric groupings falling within the generic disclosure. This invention therefore includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

The scope of the invention is not limited by the description of the examples. Modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific examples which have been presented by way of example.